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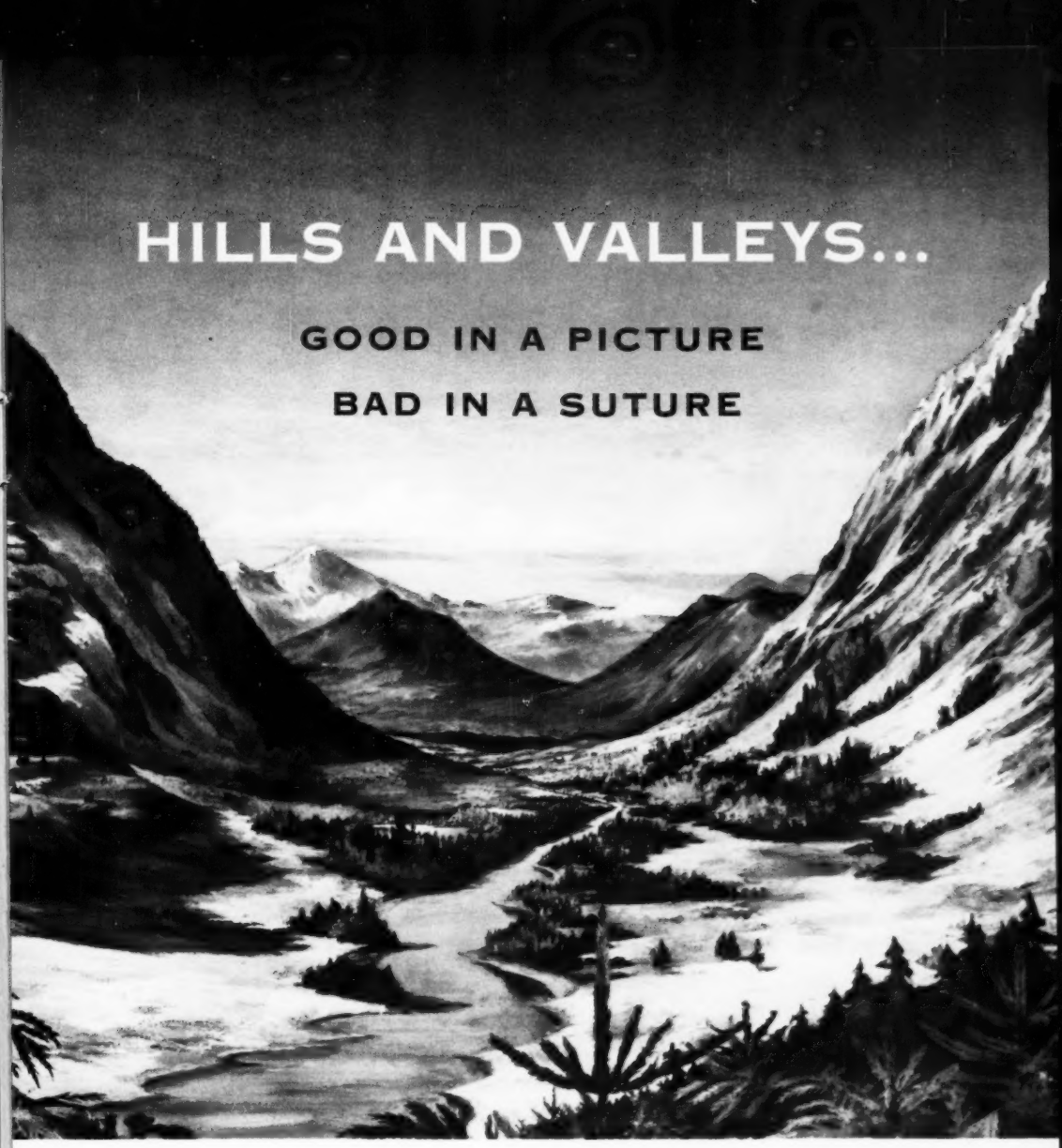

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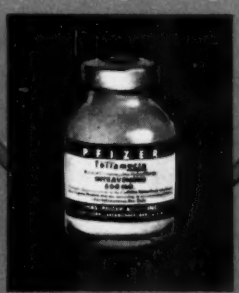

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Reiss, E., et al.: A. M. A. Arch. Surg. *64*:5 (Jan.) 1952.

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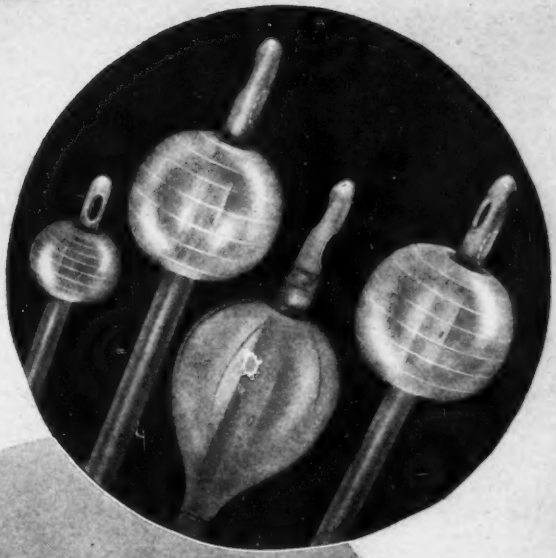

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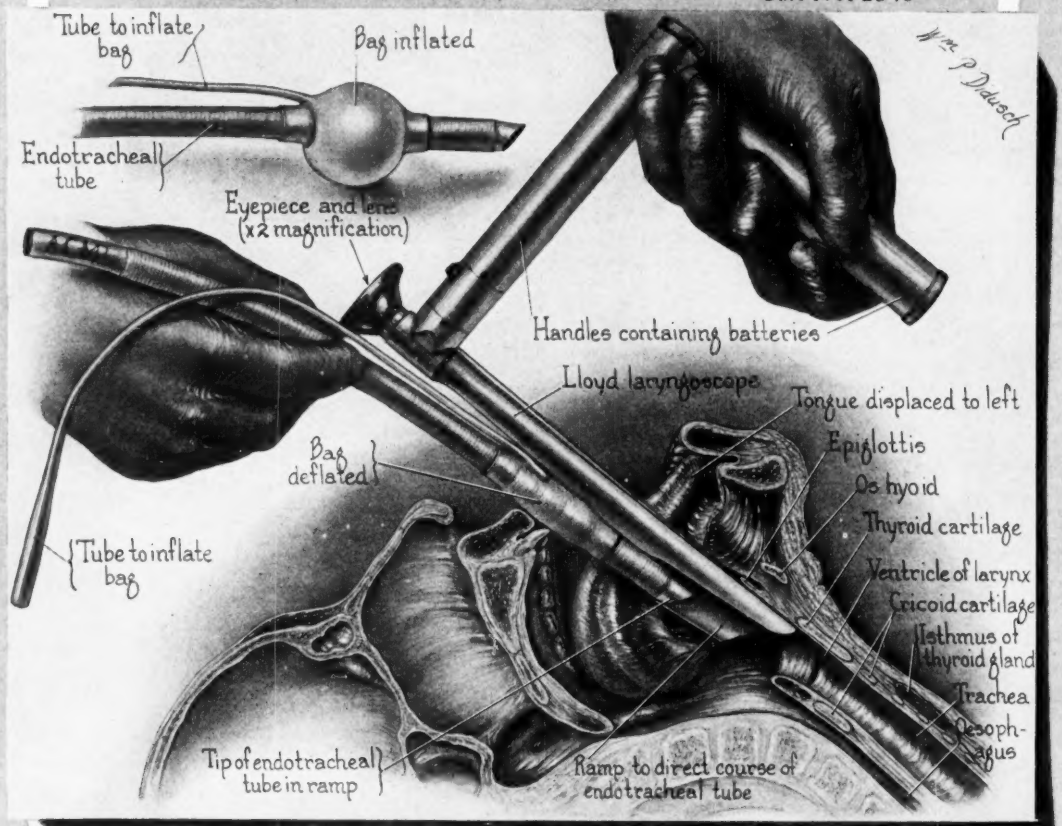

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VOLUME 67 AUGUST 1953 NUMBER 2

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Editorials

COLLOIDAL PARTICLES FOR RETROPERITONEAL IRRADIATION

AS UROLOGIC surgeons, we have followed with interest the clinical application of Hahn's pioneer work [1] to the interstitial injection of radioactive colloids,[2] as in carcinoma of the cervix by Sherman and his co-workers,[3] and to their use by direct infiltration in prostatic cancer by Flocks.[4] In this issue of the ARCHIVES OF SURGERY, a further extension of their use is described. Berg, Christopherson, Isaacs, and Bryant [5] have measured the take-up of radioactive colloidal particles (Au^{198}) by the lymph nodes after injection into the fundus of the bladder and found probable therapeutic concentrations of radioactivity in the iliac, aortic, and hypogastric nodes.

We, too, have been trying to irradiate nodes (in our case, the retroperitoneal) with these substances.[6] It occurred to us that if particulate radioactive material were placed in the presacral space (as in retroperitoneal pneumography), it would be picked up by the retroperitoneal lymphatics and carried to the preaortic and renal nodes as well as the presacral and iliac groups. Dog experiments with inert material (HgS) showed good pick-up as high as the subclavian nodes, without

1. Hahn, P. F., and Sheppard, C. W.: The Therapeutic Use of Radioactive Elements in Malignancy, Ann. Int. Med. **28**:598, 1948. Hahn, P. F.; Goodell, J. P. B.: Sheppard, C. W.; Cannon, R. O., and Francis, H. C.: Direct Infiltration of Radioactive Isotopes as a Means of Delivering Ionizing Radiation to Discrete Tissues, J. Lab. & Clin. Med. **32**:1442, 1947. Meneely, G. R.; Kory, R. C.; Auerbach, S. H., and Hahn, P. F.: Distribution of Radioactive Colloidal Gold Following Intrapulmonary Adminstration, Federation Proc. **10**:365, 1951. Hahn, P. F.: A Manual of Artificial Radioisotope Therapy, New York, Academic Press, 1951. Hahn, P. F.; Rouser, G.; Brummitt, H.; Moorehead, J., and Carothers, E. L.: The Drainage of Radioactive Silver Colloids by the Lymphatics Following Intrapulmonary Administration in Dogs, J. Lab. & Clin. Med. **39**:624, 1952.

2. Allen, H.; Hempelmann, L. H., Jr., and Womack, N. A.: The Effect of Insoluble Radiophosphorus (Chromium Phosphate) When Applied Interstitially in the Treatment of Adenocarcinoma of the Mamma in Mice, Cancer Res. **5**:239, 1945.

3. Sherman, A. I.; Nolan, J. F., and Allen, W. M.: The Experimental Application of Radioactive Colloidal Gold in the Treatment of Pelvic Cancer, Am. J. Roentgenol. **64**:75, 1950.

4. Flocks, R. H.; Kerr, H. D.; Elkins, H. B., and Culp, D.: Treatment of Carcinoma of the Prostate by Interstitial Radiation with Radio-Active Gold (Au^{198}): A Preliminary Report, J. Urol. **68**:510, 1952.

5. Berg, H. F.; Christopherson, W. M.; Isaacs, A. M., and Bryant, J. R.: Localization of Radioactivity in Regional Lymph Nodes, A. M. A. Arch. Surg. **66**:228 (Aug.) 1953.

6. Hinman, F., Jr.; Miller, G. M., and Ng., E., in discussion on O'Conor, V. J.; Bulkley, G. J., and Cooper, J. A. D.: Intraprostatic Injection of Radioactive Colloids: An Experimental Study, read at the 48th Annual Meeting of the American Urological Association, St. Louis, May 11-14, 1953.

spread outside the body cavity. Injection into guinea pigs proved the same distribution and also demonstrated that the particles were removed from the presacral space in from 7 to 11 days. Two patients were given carbon particles by the same route; at radical node dissection two days later, both showed deposition of the carbon in iliac nodes (the time interval being presumably inadequate for further distribution). John Benjamin,[7] too, in experiments soon to be published, has found that radioactive colloids are carried to the preaortic and renal nodes if injected either into the testis or into the spermatic cord.

The interstitial use of radioactive particles seems to me much more rational than attempting to destroy a tumor mass by direct infiltration. If the lymphatic spread of the tumor is massive, of course, neither method can be effective, since uniform distribution cannot be achieved. But if the nodes are not packed with tumor, interstitially injected particles will be carried to them and can destroy the fresh tumor cells. The patient with testis tumor without palpable nodal metastasis seems the ideal candidate for this form of irradiation, either as a preparation or as a substitute for radical node dissection. The approach is still experimental because of the possibilities of causing damage to normal tissues (such as the ureters and rectum), but it promises to be clinically useful. FRANK HINMAN JR., M. D.

7. Benjamin, J.: Personal communication to the author.

IS A SCIENTIFIC PROGRAM SUFFICIENT?

R. K. GILCHRIST, M.D.
CHICAGO

THE PROGRAMS of this and other medical and surgical societies are designed to present new ideas and methods of treatment of disease or to evaluate procedures which are in vogue. The numerous meetings of these societies are well attended and should be considered to be postgraduate courses. They are well worth while. On the whole, our programs should continue to be directed in the same general pattern. However, is this scientific program sufficient?

In the past few years physicians individually and collectively have been forced to justify their customs and practices to an ever-increasing degree before the attacks of bureaucrats, welfare groups, professional philanthropic groups, government agencies, organized trade associations, and the press, in spite of the magnificent advances made in the medical sciences and in the care of the sick. We have recently been forced to hire a group of public-relations experts to help us halt the precipitous trend toward socialized medicine.

The attacks are due largely to the rapid advances in all technological fields plus the equally rapid changes in sociological and economic problems of the nation. Our detractors rightly assume that the medical profession is responsible for scientific medical advancement, the actual care of the patient, and also for formulating programs which will help meet every economic and sociological problem having to do with the care of the sick.

The American Medical Association is the policy-making body. Almost every practicing physician is a member. Final policy is formulated by the elected officers of the national association. These officers earn their living by practicing medicine. Most of us not only have been content to let them make the final decision as to policy but also have expected them to anticipate the various ancillary problems facing us and to guide us in solving them. We have been too willing to "let George do it." The members of the specialty societies, who should be better informed than most as to the implications of trends and practices pertaining to their special fields, have probably been among the worst offenders in this respect.

We have repeatedly been forced to take a defensive stand and finally to adopt a policy which has first been pushed by nonprofessional groups, as in the case of Blue Cross. Our troubles lie not with the officers of our national organization, but with us as individuals, because we have not informed ourselves sufficiently regarding the numerous problems which now confront us. Published accounts will not be read by most of us. What better means could be found to help crystallize thought

Presidential address read at the Tenth Annual Meeting of the Central Surgical Association, Chicago, March 6, 1953.

on a national level than a forty-five minute to one hour discussion of some timely problem by each of the more than two hundred specialty or geographic societies at its annual meeting?

There are a great number of problems which affect our practice and the care of the patient which could profitably be discussed by a group such as ours. These might be classified into several broad categories.

Our most pressing problem is the shortage of graduate nurses. A vigorous attack on the various factors which contribute to the shortage is needed. We surgeons and physicians generally could help formulate and implement broad policies which would assist the nursing profession, the hospitals, and the government to a solution.

First, we might consider the problems relating to a better use of the already trained graduate nurses. In 1951 there were 223,719 registered nurses working in nonfederal hospitals and schools of nursing.[1] Of these, 23,655, or ten per cent, were working part time, an increase of twenty-one per cent from the preceding year. Actually, almost one-fifth of all general-duty nurses were working only part time in 1951. There were 190,026 registered nurses twenty to forty-nine years of age who were inactive, a number almost equaling all the active nurses working in nonfederal hospitals and schools of nursing. A concerted effort by physicians and other groups concerned should make it possible to encourage an even larger number of inactive nurses regularly to spend part or entire days in nursing.

Industry and labor proudly proclaim their industrial medical programs. The President's Commission on the Health Needs of the Nation (Vol. 1; p. 66) states that ninety per cent of plants having more than five hundred employees and forty-three per cent of smaller plants have in-plant medical services. The in-plant medical services almost all employ one or many graduate nurses. In many cases, because of the requirements of a union contract, more nurses are employed than are ever needed, a situation similar to that seen by most of us while we were members of the armed services in World War II. A discussion of this particular problem by one of our societies might well result in a program which would allow for the replacement of many of these trained nurses by clerks and assistants; or, in many cases, the pooling of services by adjoining plants could result in better care with fewer nurses. This program would be to the financial advantage of management, and it should be obvious to labor that the nurses freed to return to active nursing would be to the advantage of every union member who needs hospital care.

The second aspect of industrial nursing concerns management. In 1951 there were 14,323 registered nurses employed in industry. When one considers that only sixty per cent of registered nurses are active, it seems obvious that more than 1,400 registered nurses must be trained each year simply to act as replacements for the number now employed by industry. The cost of training these nurses is largely borne by the hospitals. It seems obvious that industry is not carrying its share of the financial burden here. It should be possible to educate management to its responsibility and to encourage industrial concerns at least to reimburse the schools of nursing for this expense, a just debt. If physicians generally lent our support to such a program, industry might be induced to pay for scholarships in nursing schools to help meet this need.

1. Facts About Nursing, American Nurses Association, New York, 1952.

The equally large drain on hospital finances and on the graduate-nurse supply by the Veterans Administration (14,500 in 1952) and United States Public Health Service (25,788) is another problem. Establishment of nurses' training schools by Veterans Administration hospitals might help. Certainly the justification for the premium salaries paid by the Veterans Administration to nurse the indigent, non-service-connected two-thirds of their patients would be worth considering.

The second aspect of the graduate-nurse problem has to do with training. There seems to be a strong tendency for the nurses' training program to give courses which are primarily suited to training "supervisory nurses." Emphasis is more and more on theory and less and less on bedside nursing. Since most schools of nursing operate at a deficit, the work done by the student nurse being insufficient to pay for the entire cost of her training, such training is a poor investment at present. However, if members of the nursing profession are to face the problem and realize that they cannot train enough graduate nurses to meet the need and that their function is to train supervisors who will direct the activities of nurses' aides, practical nurses, and similar workers, then their program is moving in the right direction. Such a long-range plan requires a vigorous program to recruit and to train additional nurses' aides and practical nurses. In 1951 the auxiliary nursing personnel almost equaled the number of registered nurses employed in general hospitals. The medical profession must take a part in this program, as our cooperation will make the transition easier and will help to recruit candidates for the practical-nursing schools.

Our societies might consider the various financial aspects of medical care. The insurance problem is being actively studied. The problem of "fee splitting" is being attacked by both the American College of Surgeons and the Bureau of Internal Revenue, and most specialty societies will probably choose to help the attempt to enforce the principles of medical ethics of the American Medical Association, which, under Article VI, Section 5, include the statement, "The giving or receiving of a commission by whatever term it may be called or under any guise or pretext whatsoever is unethical."

The care of the indigent will be with us as long as we are independent. With the change in the economic status of most of the white-collar class because of the tax burden and the more favorable economic status of the so-called laboring classes, this problem should be a good one to consider. The forty-hour week has added a tremendous financial burden, and it has also increased the scarcity of trained nurses and technicians. Seemingly, only the physician is expected to work more than forty or forty-four hours a week. Since most of us devote fifteen to forty per cent of our time to charity work, it would seem logical to expect other segments of the population to carry their share of the load. The volunteer lay workers in hospitals and clinics are almost entirely recruited from the so-called white-collar class in spite of the favorable financial position of most of the members of the unions. The unions have been especially slow in assuming their share of the responsibility for the care of the indigent. A consideration of the nonprofessional charity services throughout the country attempting to show how various segments of our population discharge this responsibility might result in the unions taking an active part. They could assign hours of work instead of dollars to carry their just share. Surely there are

union leaders who would be far-sighted enough to realize that such action is their duty and, also, that it would tend to lessen the increasingly severe criticism of selfishness which is levelled at them.

The training of nurses' aides, technicians, interns, and residents could be simplified if a concerted effort were made to standardize the names and types of surgical instruments, dressings, and so on. These are now named after a large number of surgical individualists, each hospital tending to perpetuate the name of some surgical great or near-great. An effort should be made to formulate a uniform nomenclature and to standardize all possible types of mechanical devices. This procedure would cut manufacturing costs and also make it possible for nonprofessional help and house officers to shift from one institution to another without confusion.

The training of specialists presents an ever-increasing number of problems. We might review the entire program of surgical training in the light of the economic situation. It seems obvious that much of the problem of "free beds," which could be used to give the resident responsibility, is one of a lack of a national plan to use all our teaching services to their best advantage. Does it not seem wise to aim toward a program under which each resident receives his first year and a half or two years of training in a well-organized "private teaching hospital"? After this indoctrination in the basic science and laboratory service and after a year and a half or two years under close supervision, in which the resident learns how well this specialty can be run, he is transferred to a hospital supported by public funds, either a Veterans Administration hospital or a county or community hospital. Here his supervision should be at least as close as it is now. However, with the background of private-hospital experience, he will be aware of the economic side of medicine; he will be more mature, so that he can assume the care of patients in a progressive manner; the cost to the public will tend to be reduced appreciably, since even the most efficient Veterans Administration and other tax-supported hospitals have a much slower turnover than do private institutions. Also, the tendency to let resident surgeons operate on patients in the earlier part of their training period, when they are not yet mature, will be lessened. Such a program could be developed and would benefit medicine, and it need not result in a loss of either prestige or income to the teachers responsible for the various resident-training programs.

Another problem associated with the training of specialists is the make-up of the certifying boards. It seems obvious that these should not be self-perpetuating groups. The new members of the various boards should be selected by independent groups and not elected by the members of the board. This program would help to prevent empire building. The problem is not present generally, but it is present with certain groups and it should be corrected.

The intern problem has become acute in the past few years. An excellent report regarding this has been made by the Advisory Committee on Internship to the Council on Medical Education and Hospitals of the American Medical Association.[2]

As the internship was originally designed, the patient was cared for by the physician with the intern as his agent. Today, with the broad expansion of resident-training programs, the sequence in the teaching hospitals is patient, student clerk, intern, junior resident, resident, possibly an associate, and the attending physician, a

2. Report of Advisory Committee on Internship to the Council on Medical Education and Hospitals of the American Medical Association, J. A. M. A. **151**:499 (Feb. 7) 1953.

most remarkable dilution. Today the four-year student is better informed than the graduate was twenty-five years ago. Medical schools should be able to develop services in teaching hospitals so that four-year students would live in hospitals and take over intern functions, with a somewhat smaller service per man in order to allow more time for study. The present intern might then choose one or two courses. If he wished to go into general practice he might take an internship in a non-university hospital near where he intended to practice; if he expected to continue his studies in order to qualify for certification by a specialty board he would be fitted into such a program at an earlier date than heretofore. Some such plan would help lessen the intern shortage. It would tend to shorten the long period of training needed to train specialists. It would tend to lessen the physician shortage by shortening the training period by one-half to one year.

Another live subject is the economic problem in anesthesia. This problem is closely related to surgery and surgeons, and the surgical societies should help formulate a program which would assure the anesthetist an adequate income and which would provide sufficient trained anesthetists, probably by a rapid increase in trained nurse anesthetists, since there will not be a sufficient number of physician anesthetists to meet the need in the foreseeable future. The financial rights of the patient should also be considered, since programs which deny the patient insurance payments for this service will eventually bring discredit upon the entire profession.

With the seemingly perpetual state of military emergency, the need for supplying physicians for the armed services is severe. The plan to unify the medical departments of the Army, Navy, and Air Force has not been pushed, and while there is less waste of physicians now than during World War II, there is still a severe and needless waste. A monthly report made directly to an appropriate committee of the American Medical Association by each physician inducted into the armed services might help cut this waste of time. In view of the double jeopardy imposed upon the medical profession by the doctor-draft law, this report would not seem unreasonable. The direct information might well result in drastic reductions in many places. Provision for the report could be provided by Congress in spite of inflexible military procedure.

Another problem caused by the doctor-draft law is the question as to whether any physician should be exempt from service. Some local medical societies have taken the stand that no physician is essential and that any physician who can carry on an active practice can perform a similar function for the armed services. A sudden removal of all "essential" classification would badly disrupt some medical schools. Possibly a maximum deferment of two years might be considered, the members of the medical profession of each state being kept informed as to the identity of those who are so classified.

The laws of most states allow osteopathic physicians to carry on a medical practice with a little limitation. These osteopathic physicians were not inducted into the armed services. The problem of their exemption from responsibility on a national level is partly our fault. It would be well worth while to attempt to arrive at an agreement with the osteopathic schools as to their training. Possibly they should be urged and helped to raise their standards to qualify as Class A medical schools by a certain date, after which all differential between the two types of practice might be lifted. It seems reasonable to raise the standards for their new graduates and to

accept the existing fact of near equality and thus present a united front to the public, as well as to allow their members to assume their share of the military responsibility.

There are numerous other problems which face our profession, many of which would benefit from a consideration by specialty groups. The question of unnecessary surgical operations would probably be better considered by a limited geographical study or by some smaller group than on a national basis. Surgical practices in the "Hill Burton hospitals" have added a new problem. A companion problem is that having to do with charlatans and incompetents. The control of these two groups might be considered to be a part of the problem of malpractice insurance, which is becoming acute.

Public relations concern us all. Each and every one of us should help with the work of our grievance committees. The public should be informed of their existence and how they function and what they do. The surgical societies should set up procedures to help local grievance committees meet complaints of overcharging.

The additional list of problems which affect us all is very long. Their solutions are not easy. It is too much to expect the officers of the American Medical Association to keep all these problems under constant attack. It seems logical that the specialty and regional societies should devote some time to a formal discussion of one of the current ancillary problems at each of its annual meetings. If this were done and the various societies did not overlap their programs, the programs would help the national association meet current problems with more timely and forceful support from the entire medical profession. The possibility of such a result would justify the conclusion that a scientific program is not sufficient.

ALPHA-TOCOPHEROL AND ALPHA-TOCOPHEROL PHOSPHATE IN THE PROPHYLAXIS OF THROMBOEMBOLISM

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IN THE first seven months of 1949, thromboembolic disease developed postoperatively in nine patients in the surgical service of the Snyder-Jones Clinic, Winfield, Kan., and two of these nine patients died with pulmonary embolism. During the summer of 1949, we learned of the work later reported by Ochsner, DeBakey, and DeCamp, and by Kay and his co-workers[1] on blood antithrombin levels and the use of alpha-tocopherol in raising the blood antithrombin levels. Beginning Aug. 1, 1949, an attempt was made to give alpha-tocopherol acetate, 200 mg. every eight hours to all patients undergoing major surgery. Medication was started prior to surgery whenever possible and continued throughout the postoperative period in the hospital. In addition, patients were given calcium gluconate, 10 cc. of a 10% solution intravenously, every 48 hours, starting sometime in 1950. Still later, alpha-tocopherol phosphate became available for intramuscular injection and was prescribed postoperatively in a dose of 100 mg. every eight hours until the patient could tolerate alpha-tocopherol acetate by mouth.

During the two years of the study, 925 major surgical patients in our surgical services were included. Of these, 205 received both alpha-tocopherol and calcium, 366 received alpha-tocopherol alone, and 354 patients received no alpha-tocopherol.

In the 14-year period between January, 1939, and January, 1953, there were 17,916 patients admitted to the surgical services in the St. Mary's and William Newton Memorial Hospitals, Winfield, Kan. According to the records, thromboembolic disease developed postoperatively in 72 of these patients, and in 17, death resulted from pulmonary embolism. Most of the patients with thromboembolic disease and all but one with fatal pulmonary embolism were patients in the surgical

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1. Ochsner, A.; DeBakey, M. E., and DeCamp, P. T.: Venous Thrombosis, read before the Thirteenth Congress of the International Society of Surgery, New Orleans, Oct. 10-15, 1949. Kay, J. H.; Hutton, S. B.; Weiss, G. N., and Ochsner, A.: Studies on an Antithrombin Test for the Prediction of Intravascular Clotting, read before the Thirteenth Congress of the International Society of Surgery, New Orleans, Oct. 10-15, 1949. Ochsner, A.; Kay, J. H.; DeCamp, P. T.; Hutton, S. B., and Balla, G. A.: Newer Concepts of Blood Coagulation, with Particular Reference to Postoperative Thrombosis, Ann. Surg. **131**:652-665 (May) 1950.

service of the Snyder-Jones Clinic. Throughout this period, early ambulation, leg exercise, deep breathing exercises, and the avoidance of pillows under the lower extremities were prescribed for all postoperative patients. Between 1945, and Aug. 1, 1949, prophylactic superficial femoral vein interruptions were done in a small selected group of patients. Since 1945, superficial femoral vein interruptions have been performed on almost all patients in whom phlebothrombosis developed and in a few with thrombophlebitis.

Table 1 compares the incidence per 100,000 of thromboembolic disease and fatal pulmonary embolism in the two Winfield hospitals with those of the Charity Hospital, New Orleans, as reported by Ochsner,[2] and of the Vicksburg Hospital, Vicksburg, Miss., as reported by Wigginton, Parsons, and Purks.[3] Incidences in the medical service and in the obstetrical service are shown for Charity Hospital and for the two Winfield hospitals. It may be seen that the reported incidence of

TABLE 1.—*Comparative Rates per 100,000 of Cases of Thromboembolic Disease and of Cases of Fatal Pulmonary Embolism*

	Surgical Patients, No.	Medical Patients, No.	Obstetrical Patients, No.
Charity Hospital, New Orleans			
Thromboembolic disease	239	217	97
Fatal pulmonary embolism	90	173	17
Vicksburg Hospital, Vicksburg, Miss.			
Thromboembolic disease	433	...	..
Fatal pulmonary embolism	76	...	..
Two hospitals, Winfield, Kan.			
Thromboembolic disease	396	296	79
Fatal pulmonary embolism	95	116	0

thromboembolic disease in the surgical service in Vicksburg Hospital and in the two Winfield hospitals was much higher than that at Charity Hospital. The incidence of fatal pulmonary embolism, however, was 95 per 100,000 in our hospitals, as compared with 90 per 100,000 at Charity Hospital and 76 per 100,000 at Vicksburg Hospital. Our medical service reported a higher incidence of thromboembolic disease but a definitely lower incidence of fatal pulmonary embolism than that of the medical service at Charity Hospital.

Table 2 presents data on patients admitted to the surgical services of our two hospitals. Patients undergoing major general surgery, gynecological surgery, genitourinary surgery, and traumatic surgery are all included. The cases are divided according to three different periods: the first period covering 10 years 7 months prior to the institution of the study with alpha-tocopherol; the second, the 2 years during the study, and the third, the 17 months following the termination of the alpha-tocopherol study. It may be seen that the incidence of thromboembolic disease was

2. Ochsner, A.: Cause and Prevention of Thromboembolism, Postgrad. Med. **10**:394-402 (Nov.) 1951.

3. Wigginton, R. C.; Parsons, W. H., and Purks, W. K.: Thrombosis and Embolism: The 5 Year Experience of Small General Hospital, Ann. Surg. **129**:784-796 (June) 1949.

practically the same throughout the three periods. However, deaths from pulmonary embolism occurred more frequently during the period of the study than during either of the other two periods.

Data on patients admitted to the medical service during these same three periods are shown in Table 3. The incidence of fatal pulmonary embolism did not increase during the period 1949 to 1951 in the medical service as it did in the surgical service, but did show an increase in the last 17-month period, while in the surgical service

TABLE 2.—*Data on Surgical Patients Admitted Between 1939 and 1953*

	Total No. of Patients	Patients with Thromboembolic Disease	Deaths from Pulmonary Embolism
1/1/39- 8/ 1/49	12,150	48 (0.39%)	8 (0.065%)
8/1/49- 8/ 1/51	3,245	3 (0.40%)	8 (0.247%)
8/1/51-12/31/52	2,521	11 (0.44%)	1 (0.040%)

TABLE 3.—*Data on Medical Patients Admitted Between 1939 and 1953*

	Total No. of Patients	Patients with Thromboembolic Disease	Deaths from Thrombo-embolism
1/1/39- 8/ 1/49	9,089	30 (0.330%)	9 (0.099%)
8/1/49- 8/ 1/51	2,574	7 (0.270%)	3 (0.116%)
8/1/51-12/31/52	2,179	4 (0.183%)	4 (0.183%)

TABLE 4.—*Data on Obstetrical Patients Admitted Between 1939 and 1953*

	Total No. of Patients	Patients with Thromboembolic Disease	Deaths from Thrombo-embolism
1/1/39- 8/ 1/49	5,511	5 (0.091%)	0
8/1/49- 8/ 1/51	1,189	1 (0.084%)	0
8/1/51-12/31/52	910	0	0

TABLE 5.—*Data on Major Surgical Cases (Study Group 1949-1951)*

	Patients Treated, No.	Patients with Thromboembolic Disease	Deaths from Pulmonary Embolism
Alpha-tocopherol and calcium	205	2 (0.98%)	1 (0.49%)
Alpha-tocopherol	366	6 (1.64%)	3 (0.82%)
No alpha-tocopherol	354	4 (1.13%)	3 (0.85%)
Total	925	12 (1.30%)	7 (0.76%)

there was only 1 death in 2,521 admissions, an incidence of 0.04%. Table 4 gives for comparison the incidence of thromboembolic disease and fatal pulmonary embolism in obstetrical patients during this same period. A very low incidence of thromboembolic disease and a complete absence of fatalities are noted in that service.

Table 5 presents data on the major surgical cases included in the study group between 1949 and 1951. The 205 patients receiving both alpha-tocopherol and calcium as a prophylactic measure showed the lowest incidence of thromboembolic disease and fatal pulmonary embolism. When alpha-tocopherol was used alone, the

incidence of fatal pulmonary embolism was essentially the same as when no alpha-tocopherol was administered. However, in carefully analyzing the cases in which thromboembolic disease developed in this group, some very interesting data are encountered. The one patient who died of pulmonary embolism, among those receiving alpha-tocopherol and calcium, received this medication for one week following a subtotal gastrectomy. He then refused medication. Six days after the discontinuance of alpha-tocopherol and calcium, dyspnea and signs of phlebothrombosis developed; a superficial femoral vein interruption was accomplished. The next day he died of a pulmonary embolism.

Of the three patients dying of pulmonary embolism in the group that received alpha-tocopherol alone, two had adequate continuous therapy. The third patient, an 87-year-old white woman who had been a hospital patient three and one-half years prior to her death (initially for hip fracture, then for senility), fell out of bed, fracturing her tibial plateau. The leg was immobilized in plaster two months before her

TABLE 6.—*Incidence of Thromboembolic Disease and Fatal Pulmonary Embolism in 925 Patients Undergoing Major Surgery**

	Incidence of Thromboembolic Disease	Deaths from Pulmonary Embolism
Adequate alpha-tocopherol and calcium	1 (0.49%)	0
Adequate alpha-tocopherol	2 (0.55%)	2 (0.55%)
Inadequate or no alpha-tocopherol	9 (2.51%)	5 (1.39%)

* Study group, 1949-1951.

TABLE 7.—*Data on Major Surgical Patients (841) Admitted Between August, 1951 and January, 1953*

	Incidence
Thromboembolic disease	11 (1.31%)
Deaths from pulmonary embolism	1 (0.12%)

death. She was given alpha-tocopherol therapy for a month. This was discontinued a month before her death from pulmonary embolism.

Taking the above-mentioned factors into consideration, another table was prepared. From Table 6 it is seen that there was a far greater incidence of thromboembolic disease and fatal pulmonary embolism in the group which received inadequate or no alpha-tocopherol. However, we do not believe that from the results in this small group of cases one can assume that adequate alpha-tocopherol and calcium therapy can be depended upon to prevent thromboembolic disease and fatal pulmonary embolism.

Table 7 gives the incidence of thromboembolic disease and fatal pulmonary embolism in our major surgical cases from Aug. 1, 1951, to Jan. 1, 1953. Although there were 11 patients with peripheral thromboses, only 1 of them died. This patient died after a prolonged illness resulting from a removal of common duct stone, complicated by the development of a duodenal fistula during her postoperative course and also by acute peritonitis. Her death did not come suddenly, but definite antemortem clots were found in both pulmonary arteries.

SUMMARY

The reported incidence of thromboembolic disease in the surgical services of St. Mary's and William Newton Memorial Hospitals, Winfield, Kan., is considerably higher than that reported in the surgical service of Charity Hospital, New Orleans, and not quite so high as the reported incidence in the Vicksburg Hospital, Vicksburg, Miss.

The incidence of fatal pulmonary embolism was slightly higher in the Winfield hospitals than in Charity Hospital and definitely higher than that in the Vicksburg Hospital.

In a two-year period, 925 major surgical patients in the two Winfield hospitals were included in the study group. Of these patients, 205 received alpha-tocopherol and calcium; 366, alpha-tocopherol alone, and 354 received no alpha-tocopherol. During the period of this study our incidence of fatal pulmonary embolism was much higher than in the 10 years 7 months preceding the study and in the 17 months following the study. The incidence of thromboembolic disease was almost constant throughout the three periods.

In analyzing the cases in which thromboembolic disease developed during the study period, it was found, however, that in only one patient receiving adequate alpha-tocopherol and calcium thromboembolic disease developed, and this patient survived. In only two patients receiving alpha-tocopherol orally did thromboembolic disease develop, and both died. Those receiving inadequate or no alpha-tocopherol showed a much higher incidence of both thromboembolic disease and fatal pulmonary embolism.

In spite of these apparently favorable prophylactic results, no conclusions can be drawn from this study of a comparatively small group of patients.

USE OF BISHYDROXYCOUMARIN (DICUMAROL) FOR PREVENTION OF POSTOPERATIVE THROMBOEMBOLISM

A Study of Twenty-Seven Hundred Consecutive Surgical Patients

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THROMBOEMBOLISM is a disorder of the normal circulation of the blood which results in complete or partial obstruction of large vessels and may or may not result in detachment of a portion of the thrombus with its lodgment at another site. Thrombosis due to intravascular clotting of the circulating blood may occur in any portion of the circulatory system. Venous thrombosis, with which we are most concerned in this study, occurs most prominently in the veins of the lower extremities; in the veins of the pelvis, including the parauterine and paraprostatic veins, and occasionally in the veins of the upper extremities.

The entity of intravascular thrombosis has been recognized since the time of Hippocrates and Galen. Virchow, in 1846, was one of the earliest authors to advance the theory and demonstrate that pulmonary emboli arose from thrombi in the pelvic or femoral veins. Early in the 20th century repeated reports emphasized the increasing incidence of vascular thrombosis and embolism in the postoperative patient.[1]

The formation of an intravascular clot is advanced by circulatory stasis, alteration of the component parts of the clotting mechanism, and direct or indirect trauma to the vascular endothelium. In the patient undergoing a major surgical procedure, all the factors predisposing to clot formation are present. Despite the awareness of the medical profession of the occurrence and potentially fatal outcome of this pathological entity, the incidence has been on the increase since the time of Hippocrates.

We agree with other investigators that differentiation by clinical signs and symptoms between phlebothrombosis and thrombophlebitis is often difficult or

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From the Department of Surgery of the Buffalo General Hospital and the University of Buffalo School of Medicine.

1. Beckman, E. H.: Complications Following Surgical Operations: A Report of the Complications and Deaths in a Series of 5,835 Surgical Operations Performed in the Mayo Clinic, St. Mary's Hospital, in the Year 1912, Ann. Surg. **57**:718-729, 1913. Miller, R. H., and Rogers, H.: Postoperative Embolism and Phlebitis, J. A. M. A. **93**:1452-1456 (Nov. 9) 1929. Wilson, L. B.: Fatal Postoperative Embolism, Ann. Surg. **56**:809-817, 1912.

impossible. The two conditions may exist simultaneously in various stages of their development, and, furthermore, it is felt that the embolic potentials of these entities are approximately the same. We assume, therefore, that the differentiation is academic and unwarranted clinically. We will discuss this complication only in terms of thrombophlebitis.[2]

Venous thrombosis of the lower extremity is diagnosed in approximately 1 to 2% of all hospitalized patients. In approximately one-half of these patients pulmonary emboli will develop, of which more than 20% will be fatal. Thromboembolism today ranks as one of the foremost causes of death in the postoperative patient over the age of 40. In spite of recent advances in medicine, thromboembolic complications in postoperative patients are increasing and account for approximately 8% of all postoperative deaths.[3]

In a six-year study at the Buffalo General Hospital (1944-1949), it was found that 33,882 patients underwent operative procedures, of whom 1.96% died postoperatively and 6.3% of these died because of pulmonary embolism. This analysis closely approximates similar reports in the literature. The figure might well be higher, because, with the earlier ambulation and discharge of hospitalized patients, the hospital records do not reveal how many fatal pulmonary emboli have occurred at home.

That this pathological entity is ever present and seemingly on the increase is noted from the reports in the literature and is attested by the variety and number of therapeutic methods that have been advocated to prevent and treat venous thrombosis, particularly that involving the lower extremity and pelvis, from whence the majority of fatal pulmonary emboli arise. Early ambulation of the postoperative patient, bicycle exercises for the bedridden patient, elastic bandages or stockings for the patient with varicosities, weight reduction, and use of thyroid extract have been advocated and widely utilized. That these methods have not materially reduced the incidence of venous clotting and pulmonary embolism is obvious from a survey of the literature.

The prophylactic and therapeutic ligations of the superficial femoral veins advanced by Allen and others [4] have also not reduced the incidence of venous

2. (*a*) McLachlin, J., and Paterson, J. C.: Some Basic Observations on Venous Thrombosis and Pulmonary Embolism, Surg., Gynec. & Obst. **93**:1-8 (July) 1951. (*b*) Allen, E. V.; Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, W. B. Saunders Company, 1946.

3. Barker, N. W.; Nygaard, K. K.; Walters, W., and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism: I. Incidence in Various Types of Operations, Proc. Staff Meet., Mayo Clin. **15**:769-773 (Dec. 4) 1940; III. Time of Occurrence During the Postoperative Period, ibid. **16**:17-21 (Jan. 8) 1941. Zilliacus, H.: On the Specific Treatment of Thrombosis and Pulmonary Embolism with Anticoagulants, with Particular Reference to the Post-Thrombotic Sequelae, Results of 5 Years' Treatment of Thrombosis and Pulmonary Embolism at Series of Swedish Hospitals During Years 1940-1945, Acta med. scandinav. 1946, Supp. 171, p. 1. Ochsner, A.; Debakey, E., and DeCamp, P. T.: Venous Thrombosis, J. A. M. A. **144**:831-834 (Nov. 4) 1950. Kirby, C. K., and Fitts, W. T., Jr.: Thromboembolic Complications in Surgical Patients, Surgery **27**:564-571 (April) 1950. Aufses, A. H., and Neuhof, H.: Causes of Death After Operation: Comparison Between Last Decade and 1920's, J. Mt. Sinai Hosp. **18**:166-178 (Sept.-Oct.) 1951. McLachlin and Paterson.[2a]

4. Allen, A. W.; Linton, R. R., and Donaldson, G. A.: Thrombosis and Embolism: Review of 202 Patients Treated by Femoral Vein Interruption, Ann. Surg. **118**:728-740 (Oct.) 1943; Venous Thrombosis and Pulmonary Embolism, J. A. M. A. **133**:1268-1274 (April 26) 1947. Allen, A. W.: The Present Evaluation of the Prophylaxis and Treatment of Venous Thrombosis and Pulmonary Embolism, Surgery **26**:1-7 (July) 1949.

thrombosis and pulmonary embolization, according to a report by Roe and Goldthwaite in 1949.[5] These authors reviewed the incidence of pulmonary embolization at the Massachusetts General Hospital in the era prior to and during prophylactic superficial femoral vein ligation. Their figures revealed no decrease in the number of pulmonary emboli and even a slight increase during the era of prophylactic venous ligations. However, the number of massive fatal pulmonary emboli was decreased. De Takats [6] and Crutcher and Daniel [7] revealed that more than 50% of pulmonary emboli arose from venous thrombosis above the inguinal ligament. McLachlin and Paterson [2a] demonstrated in autopsy material that approximately 73% of pulmonary emboli arose from venous thrombosis in large veins of the thighs and pelvis. These observations account for the fact that 40% of fatal pulmonary emboli appear before the primary source is recognized and prove the inadequacy of attempting to make the diagnosis of thrombophlebitis clinically by merely following the veins of the calves and feet. These reports lead one to conclude that a marked diminution in the number of pulmonary emboli from femoral vein interruptions is not to be expected.

PURPOSE

If good preoperative and postoperative care and gentle surgery have not decreased the incidence of postoperative thromboembolism by eliminating some of the contributing factors in the causation of intravascular thrombosis, then possibly a direct attack on the clotting mechanism itself may decrease the high incidence of thromboembolic disease with associated fatal pulmonary embolization in the postoperative patient. By such a direct approach one hopes to prevent the propagation of the thrombotic process that is already present, prevent the development of new intravascular thrombi in other parts of the vascular tree, and prevent nonfatal and fatal embolization.

The apparent failure of the measures designed to prevent circulatory stasis and thus lower the incidence of venous thrombosis in postoperative patients led us to embark on a controlled clinical experiment to study the effectiveness of, indications for, contraindications to, and management of a prophylactic anticoagulant agent administered to surgical patients. No anticoagulant agent is without its disadvantages and dangers. We assumed that, by detailed study and observations limited to a single agent, the dangers and disadvantages could be minimized and eventually the use of the agent become comparatively safe. We arbitrarily chose bishydroxycoumarin (Dicumarol) as the anticoagulant agent to be used in this study.

Since in approximately 40% of patients with a tendency toward spontaneous intravascular clotting fatal embolization developed without premonitory signs of thrombophlebitis, we thought that the prothrombin time should approximate therapeutic values, namely two and one-half to three times normal; otherwise the purpose

5. Roe, B. B., and Goldthwaite, J. C.: Pulmonary Embolism: A Statistical Study of Post-Mortem Material at the Massachusetts General Hospital, New England J. Med. **241**:679-686 (Nov. 3) 1949.

6. de Takats, G.: Management of Pulmonary Embolism, Postgrad. Med. **8**:506-509 (Dec.) 1950. de Takats, G., and Fowler, E. F.: Problem of Thrombo-Embolism, Surgery **17**:153-177 (Feb.) 1945.

7. Crutcher, R. R., and Daniel, R. A., Jr.: Pulmonary Embolism: A Correlation of Clinical and Autopsy Material, Surgery **23**:47-62 (Jan.) 1948.

of the experiment would be defeated. Realizing that the agent bishydroxycoumarin has a delayed action, we believed that in the cases in which therapeutic anticoagulant levels were desired immediately, use of a rapidly acting heparin compound in combination with bishydroxycoumarin would be the regimen of choice.

At the completion of this study we hoped not only to reduce materially the incidence of postoperative thromboembolic phenomena but also to be able to recognize clinically, with a fair degree of accuracy, the patient who had a predisposition to a spontaneous intravascular clot in the postoperative period.

MATERIAL

During a five-year period, January, 1948, to January, 1953, inclusive, 2,700 patients were admitted to the private surgical service of one of us (E. M.). All patients in this service were scrutinized for indications and contraindications for the prophylactic administration of an anticoagulant drug prior to surgery. From a critical analysis of the first 1,144 consecutive patients, the present indications and contraindications for the prophylactic use of bishydroxycoumarin were evolved, and they were applied rigidly to the study of the succeeding 1,556 consecutive patients.

METHOD OF STUDY AND RESULTS

On admission to the hospital, all the patients were classified as to indications for or against the use of bishydroxycoumarin as a measure to aid in the prevention of postoperative thromboembolic complications.

During the first two years of the study, the indications for the use of bishydroxycoumarin were not inclusive enough, as was indicated by an analysis of the untreated, or control group, of patients. Of the first series of 1,144 patients, 872 were thought to be excellent surgical risks with little reason to expect an intravascular thrombosis in the postoperative period; 272 patients were treated with prophylactic anticoagulants because they were thought to represent excellent candidates for postoperative thrombotic complications.

In the untreated group, or excellent-risk group, of 872 patients there were 41 postoperative thromboembolic complications in 35 patients, or an incidence of approximately 1 in every 25 patients. Of these 35 patients, a pulmonary embolus developed in 14, or 40%, and 3, or 21%, of those having a pulmonary embolus had a fatal outcome. Therefore, the incidence of pulmonary emboli in this group of 872 untreated patients was 1.6%, with a mortality rate of 0.34%. Of these 872 patients, clinically detectable thrombophlebitis with or without associated pulmonary embolism developed in 27, or 3.1%. Among the 272 patients who received prophylactic anticoagulants, signs of thrombophlebitis developed in 2, an incidence of 1 in 136 patients. There were no fatalities or pulmonary emboli observed in this group of treated patients (Table 1).

A survey of the 35 patients in whom thromboembolic complications developed, who had received no prophylactic bishydroxycoumarin therapy because they were felt to be good risks, revealed that 27 of the patients were over the age of 40, 26 had major operative procedures, 9 were considered to be obese, 9 had malignant neoplastic lesions, 8 had evidence of preexisting vascular disease, and 3 were confined to bed for a protracted period. Thus, 33 of the 35 patients had one or more of what we now consider to be indications in surgical patients for the prophylactic adminis-

tration of bishydroxycoumarin. Patients who did not receive the drug in the first series but who now would in the light of our final criteria are exemplified in the following two case histories.

L. K., a 25-year-old housewife, was admitted to the hospital because of lower abdominal pain of 12 hours' duration and the signs and symptoms of acute appendicitis. An appendectomy was performed without incident and the right lower quadrant and pelvis drained through a McBurney incision because of a perforation of the appendix and local peritonitis. The patient had an uneventful postoperative course until the seventh day, when a sudden pleuritic type of chest pain associated with cough and hemoptysis developed. She presented the clinical findings of a pulmonary embolus and was immediately given anticoagulant therapy. The patient left the hospital on her 18th postoperative day, clinically improved.

F. M., a 38-year-old white woman, was admitted to the service with upper abdominal pain and the signs and symptoms of recurrent cholecystitis with cholelithiasis. There was a history of idiopathic chronic ulcerative colitis. A cholecystectomy was performed, and her postoperative course was smooth until the ninth day following surgery, when the signs and symptoms of a deep

TABLE 1.—*Data on Series 1, for Whom Criteria as to Bishydroxycoumarin Therapy Were Not Sufficiently Inclusive*

	No. of Patients
Total in Series	1,144
Untreated Patients	872
Postoperative thromboembolic complications	35 (4.0%)
Thrombophlebitis	27 (3.1%)
Pulmonary emboli	14 (1.6%)
Fatalities	3 (0.34%)
Treated Patients	272
Postoperative thromboembolic complications	2 (0.74%)
Thrombophlebitis	2 (0.74%)
Pulmonary emboli	0
Fatalities	0

femoral vein thrombosis and a pulmonary embolus developed. Administration of anticoagulant drugs was started immediately, and the patient left the hospital, clinically improved, on her 21st hospital day.

The indications for the prophylactic use of bishydroxycoumarin that were derived from the analysis of the first series of cases and rigidly adhered to in the succeeding 1,556 cases are as follows:

1. A general anesthetic if the patient is over the age of 40.
2. A major operative procedure [8] if the patient is 18 years of age or over.
3. Evidence of preexisting vascular disease.
4. Obesity.
5. Postoperative confinement to absolute bed rest for an indefinite period.
6. A malignant neoplastic growth.

The absolute contraindications to the prophylactic administration of bishydroxycoumarin followed in this series are as follows:

1. Blood dyscrasias with a hemorrhagic tendency.
2. Active ulcerating lesions with evidence of hemorrhage.

8. Major operative procedures include all operations performed in the abdominal cavity and pelvis, including herniotomy and appendectomy for complicated appendicitis.

3. Operative procedures on the brain or spinal cord.
4. Hypoprothrombinemia.
5. Sensitivity to the drug.

The relative contraindications are:

1. Hepatic insufficiency.
2. Renal insufficiency.
3. Clinical evidence of vitamin C deficiency.
4. Inadequate laboratory facilities.

The majority of these contraindications, such as blood dyscrasias with hemorrhagic tendencies, hypoprothrombinemia, sensitivity to the drug, and operations on the spinal cord or brain, need little explanation. Severe liver damage may result in a failure in part of the metabolism of the drug and result in a marked and uncontrollable cumulative effect with a possibility of a fatal hemorrhagic diathesis. Renal failure in itself is not a contraindication, because the drug, unlike heparin, is not excreted by the kidney. The original study of bishydroxycoumarin and renal disease was done on kidneys completely anuric. Recent studies show that this drug is not contraindicated in the treatment of renal disease unless the patient is completely anuric.[9] It is well known that in the presence of a vitamin C deficiency there are a marked increase in capillary fragility and a tendency to spontaneous hemorrhagic lesions, contraindicating the use of an anticoagulant drug. The vast majority of the tragic experiences with bishydroxycoumarin have been caused by poor management of the therapy. A great deal of the management depends upon the accuracy and reliability of the clinical laboratory doing the prothrombin determinations.

The second series of patients studied, after the establishment of criteria for the administration of bishydroxycoumarin and contraindications to its use, numbered 1,556. In this series, 728 patients either did not have the indications for the therapy or had definite contraindications to its use. In this untreated group, signs and symptoms of thrombophlebitis developed in 2 patients, or an incidence of 1 in every 264 patients. There were no pulmonary emboli or fatalities attributable to thromboembolism. In the same series, 828 patients who had definitely recognizable indications were given prophylactic bishydroxycoumarin therapy. Clinically evident postoperative venous thrombosis developed in one patient in this treated group, but there were no demonstrable pulmonary emboli or fatalities attributable to thromboembolism (Table 2).

The total number of patients observed in the five-year period was 2,700, with 1,600 patients not receiving any prophylactic bishydroxycoumarin and 1,100 patients placed on the prophylactic anticoagulant regimen as outlined. Of the untreated group, postoperative thromboembolic lesions developed in a total of 37 patients, or 2.3%. Of the 37 patients with postoperative thrombotic lesions, pulmonary emboli developed in 14, or 38%, and were fatal in 3, or 21%.

Among the 1,100 patients treated prophylactically with bishydroxycoumarin, clinical evidence of a thrombophlebitis developed in only 3, or an incidence of 0.27%. These patients had been bedridden from two to three weeks prior to surgery. There were no pulmonary emboli or fatalities attributable to thromboembolism in the treated group (Table 3).

9. Sachs, J. J., and Henderson, R. R.: Use of Bishydroxycoumarin (Dicumarol) in the Presence of Impaired Renal Function, J. A. M. A. **148**:839-841 (March 8) 1952.

The method of administration of bishydroxycoumarin used in this study was found to be safe and efficient and gave an adequate anticoagulant effect within 48 to 72 hours in the majority of cases. Prior to surgery a bleeding and clotting time and a prothrombin time were obtained in addition to the usual clinical and laboratory studies necessary in evaluation of the patient's condition. The patients who presented indications for the therapy, as outlined, and had none of the absolute contraindications were given 200 to 300 mg. of bishydroxycoumarin the morning of surgery, and an additional 100 to 200 mg. was administered on the first post-

TABLE 2.—*Data on Series 2 (Expanded Criteria)*

	No. of Patients
Total in Series	1,556
Untreated Patients	728
Postoperative thromboembolic complications	2 (0.27%)
Thrombophlebitis	2 (0.27%)
Pulmonary emboli	0
Fatalities	0
Treated Patients	828
Postoperative thromboembolic complications	1 (0.12%)
Thrombophlebitis	1 (0.12%)
Pulmonary emboli	0
Fatalities	0

TABLE 3.—*Summary of Data on Series 1 and Series 2*

	No. of Patients
Total Studied	2,700
Total in Untreated Group	1,600
Postoperative thromboembolic complications	37 (2.3%)
Thrombophlebitis	29 (1.18%)
Pulmonary emboli	14 (0.88%)
Fatalities	3 (0.19%)
Total in Treated Group	1,100
Postoperative thromboembolic complications	3 (0.27%)
Thrombophlebitis	3 (0.27%)
Pulmonary emboli	0
Fatalities	0

operative day and none to 100 mg. on the second postoperative day. Daily prothrombin times were obtained, and the daily maintenance dose was regulated according to the prothrombin time. Once the response of the patient to the drug was ascertained, then adequate therapy could be maintained by checking the prothrombin time two to three times a week and making minor adjustments in the daily dosage. Patients on long-term anticoagulant therapy because of a thromboembolic vascular complication could be adequately managed as outpatients, with prothrombin determinations obtained every 7 to 10 days. The prothrombin time was maintained at two to three times normal, or from 25 to 40 seconds, and the prophylactic therapy was continued until the patient was fully ambulatory and for a minimum of 10 days.

A total of 1,100 patients received anticoagulant drugs prophylactically after surgery in this study. Of these 1,100 patients, hemorrhagic episodes developed in 8 while they were receiving the drug therapy. Of these episodes, five were considered minor, and simple cessation of the drug was adequate to control the bleeding. The minor hemorrhagic lesions consisted of ecchymosis, wound hematomas, petechial hemorrhages, and hematuria. Three were considered to be severe and necessitated the intravenous administration of large doses of vitamin K and transfusions of fresh whole blood. There were no fatalities from hemorrhage due to the drug therapy (Table 4).

Other modalities aimed at decreasing circulatory stasis and hemorrhagic tendencies were instituted for all patients. All were helped to walk as soon as possible after surgery. They were given 300 mg. of ascorbic acid daily, and elastic stockings were worn by all patients with varicose veins of the lower extremities. The beds were equipped with footboards to allow the bed patient freedom of motion of the extremities, and benzoimidazoline (Priscoline) and/or whisky was administered to all patients with occlusive arterial disease. Leg exercises four times a day were prescribed.

TABLE 4.—*Complications of Therapy*

	No. of Patients
Total Given Prophylactic Therapy	1,100
Mild hemorrhagic complications	5 (0.46%)
Severe hemorrhagic complications	3 (0.27%)
Fatalities	0

COMMENT AND CONCLUSIONS

The reported incidence of thromboembolism is 1 to 2% for all hospitalized patients. For surgical patients the incidence is reported as varying from 0.5 to 1.0%, with 50% of these patients having pulmonary emboli, of which 20 to 50% are fatal. In the small control series, the untreated patients in Series 1, reported here, one postoperative thromboembolic complication occurred for every 25 patients, or an incidence of 4.0%. This is a much higher percentage than that reported in the literature.

After a critical analysis of 1,144 cases in the first series, the indications and contraindications for the prophylactic use bishydroxycoumarin (Dicumarol) were established and rigidly followed in the selection of patients for therapy among the succeeding 1,556 consecutive patients.

There were 828 patients with definite indications for bishydroxycoumarin therapy, and the remaining 728 did not receive the drug prophylactically. In this second series, with the expanded indications and contraindications for the selection of patients for therapy, there were only two instances of thrombophlebitis, both of which occurred in the untreated group. There were no pulmonary emboli or fatalities due to thromboembolism. Thus, in this study, when the patients were carefully selected for bishydroxycoumarin therapy according to the criteria previously outlined, the incidence of postoperative thromboembolic complications in the untreated group fell from 4.0% to 0.27%, and there were no pulmonary emboli or fatalities in the second series of patients.

The method of administration of bishydroxycoumarin resulted in an elevation of the prothrombin time to a therapeutic range in an average of 62 hours after the institution of therapy. In less than 2% of the patients was the prothrombin time elevated over 25 seconds within the first 24 hours of therapy. There was an incidence of 0.72% of hemorrhagic complications attributable to the drug, and of these complications 0.45% were of a minor nature and 0.27% were considered severe. There were no fatalities from hemorrhage while patients were receiving the drug. The average prothrombin time maintained was 30 seconds.

We feel that, in view of the fact that there is no laboratory or clinical test yet devised that will designate with a high degree of accuracy the patient with a predisposition to vascular thrombosis, the prophylactic administration of bishydroxycoumarin to patients with the indications outlined is warranted. Furthermore, if therapy is rigidly controlled and contraindications are faithfully observed, the hemorrhagic complications of the therapy are much less frequent than postoperative thromboembolic complications and certainly are more innocuous than the end-results of the latter complications.

If such a program as that outlined were to be adopted in the surgical services of a large general hospital, the cost might necessarily be high. It would mean a considerable expansion of laboratory facilities and an increase in trained personnel. The average cost of the regimen at this time is approximately $25 to $30 a patient. However, we feel that the expense is justified when one compares it with the protracted disability arising as the result of a chronic or recurring thrombophlebitis or with sudden death from pulmonary embolization.

SUMMARY

The results of a study of 2,700 consecutive surgical patients in the selection of patients for prophylactic anticoagulant therapy have been presented.

The indications and contraindications for prophylactic anticoagulant therapy for surgical patients are outlined.

A method of prophylactic administration of bishydroxycoumarin (Dicumarol) to aid in the prevention of postoperative thromboembolism is given in detail.

Strict adherence to the indications, contraindications, and method of therapy resulted in a lowering from 4.0 to 0.27% of the incidence of postoperative thromboembolic complications in the untreated group of patients.

There were no cases of pulmonary embolism among 1,100 patients treated with prophylactic anticoagulant therapy.

DISCUSSION

On Papers by Dr. Moorman and Dr. Milch

Dr. Frank V. Theis, Chicago: I was interested in receiving the invitation from Dr. Milch to discuss his paper on the prophylactic use of anticoagulants for the prevention of postoperative thromboembolism. In the absence of reliable tests for predicting or diagnosing early thrombus formation, it was necessary for Dr. Milch to rely on clinical criteria for the selection of patients for treatment. These clinical criteria were set up after he made a thorough study of his experiences. However, the results of our monthly survey, covering a five-year period at the Presbyterian Hospital, showed that in many of our cases the thromboembolism would not have been treated according to his criteria. In fact, 10 cases occurred after minor operations, some of which were performed with use of local anesthesia. Also thromboembolism occurs more

frequently in nonsurgical and medical patients than among surgical patients so that the magnitude of the surgical procedure and the type of anesthesia are not necessarily important factors. Throughout the various groupings, recommended by Dr. Milch for treatment, we found that a number of our patients would not have been treated.

Among our untreated patients, 14 thromboembolic complications followed major surgery and general anesthesia in patients over 18 years of age; two of these patients died of pulmonary embolism. In a comparable series, 17 patients were treated with anticoagulants, and 2 of these patients died. Very little difference is shown between patients in the treated and in the untreated series.

Three questions are pertinent to the prophylactic use of bishydroxycoumarin (Dicoumarol): 1. Is the recommended therapy effective in preventing intravascular clotting? 2. Will the widespread use of mass bishydroxycoumarin therapy involve the serious danger of hemorrhage? 3. Do statistical reports support prophylactic bishydroxycoumarin therapy?

The effectiveness of bishydroxycoumarin therapy will depend upon the rapidity and control of adequate hypoprothrombin activity. An average delay of 62 hours in obtaining the therapeutic range, as just reported, will permit thrombosis to occur. Any compromise of the 10 to 20% level is really not protective. Because of the fluctuating individual tolerance of the patient to the drug, a constant effective hypothrombin activity is seldom maintained. Even with the supposedly greater accuracy of the two-stage prothrombin tests, proved thromboembolic complications have occurred during the time effective anticlotting levels had been maintained for many days.

The general use of mass bishydroxycoumarin therapy involves the serious danger of hemorrhage, especially when reliable laboratory facilities are not available. Most patients are relatively safe from serious hemorrhage at the effective anticlotting hypoprothrombin level. However, a recent autopsy showed that a massive hemorrhage from a symptomless and undiagnosed duodenal ulcer occurred when the prothrombin level was never below 25%. Another autopsy revealed a massive hemothorax due to bleeding from a small pulmonary infarct that had separated on the eighth day of therapy. With the extreme care and experience in managing the anticoagulant therapy of these patients and the reliability of the laboratory test, the serious danger of fatal hemorrhage must be recognized. Widespread prophylactic use of bishydroxycoumarin would involve inestimable risk.

Statistically, the value of bishydroxycoumarin for thromboembolism has not been conclusive. At the Mayo Clinic, anticoagulants have proved of value in preventing thromboembolic complications, but severe bleeding occurred in 2% of the cases. Allen, at the Massachusetts General Hospital, reported two deaths from hemorrhage due to bishydroxycoumarin therapy but none from pulmonary embolism in 900 cases; in a comparable series in which bishydroxycoumarin was not used, there was only one death from pulmonary embolism. Because of the extensive laboratory facilities and the experienced personnel required by the program, as outlined by Dr. Milch, his results will require further analysis and larger series of cases to justify the recommended prophylactic anticoagulant therapy program.

It is obvious that reliable and simple tests must be developed for predetermining venous thrombosis before the general use of prophylactic anticoagulant therapy can be recommended. The value and safety of the treatment must be established. This ideal is not obtainable at present. Each of us should review our cases of thromboembolism, as we have done, and decide whether the indications for prophylactic therapy as set up by Dr. Milch are warranted.

I want to show two slides.

[Slide] Here is what we have to contend with in thromboembolism. This is a femoral vein that was obtained from an autopsy specimen. The patient died of a pulmonary embolism. You can see the very limited attachment of the laminated thrombus on the tip of the valve. The only place where there is an inflammatory process is at the tip of the valve. The lumen is fairly open, and good circulation occurred through the open channel. There is no swelling of the extremity because the venous obstruction is incomplete. There is no elevation of temperature and no tenderness along the course of the vein because only very minimum inflammatory reaction is present in the valve. This is the reason why I am sure that we have more than the problem of just picking a certain type of case.

[Slide] This slide also shows just a small area of the thrombus attached to the tip of the valve of the femoral vein.

DR. JOHN A. MCLACHLIN, London, Ont., Canada: I should like to take just a minute to support aspects of both these papers.

The first paper dealt with tocopheral levels. At Westminster Hospital, in London, we carried on an investigation in which we studied the premortem alpha-tocopherol levels in a group of seriously ill people. In those who came to autopsy—95% of all deaths—we were unable to find any relationship between the alpha-tocopherol levels and the occurrence of a peripheral thrombus, the source of pulmonary embolism.

In supporting the second speaker this morning, I quite agree that we do not have any clinical tests to determine whether a patient has a thrombus or whether there is danger of a pulmonary embolus developing.

At present we have one of our personnel checking some 10 of the standard clinical tests on patients who are seriously ill.

In a separate phase we are dissecting the veins from the bifurcation of the inferior vena cava to the ankle region. None of the clinical tests are of any value in determining whether the patient has an incipient thrombus.

DR. JOHN H. OLWIN, Chicago: Thromboembolism is still a very important complication of surgery of all types.

As you know, the rationale behind the use of alpha-tocopherol and calcium was its ability to elevate the antithrombin in the plasma.

I should like to elaborate just a little on this one point.

[Slide] There are four known antithrombotic components in the blood. There is the so-called natural component, which is in the plasma and serum. There is the heparin cofactor, which is a catalytic factor. There is the fibrin, which adsorbs thrombin, and there is the release of antithrombin accelerator during prothrombin conversion.

These are not well understood. Neither is there a good assay for any one of them, much less for all four of them in the same patient.

And I think it is important that we keep our thinking straight as to why we are using these drugs. Any statistical study of a large series of patients is of importance, and I think the study of alpha-tocopherol and calcium should be continued.

I have just one word of warning, and that is that if (and as the essayists have mentioned, we still have no accurate means of anticipating thromboembolism clinically) we feel thromboembolism is likely to develop. I think we may be doing a patient a grave injury if we use the alpha-tocopherol and calcium as a prophylactic measure when we have other means which we know from experience to be reasonably effective.

Its simplicity and its lack of the bleeding hazard, of course, are very important, but it is still untried, and I think that at present is should be appraised by groups that have already started statistical studies before it is used by the profession as a whole.

DEFINITIVE TREATMENT OF FRESH INJURIES TO LARGE BLOOD VESSELS

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LARGE BLOOD vessels lie in sheltered positions in the body and are infrequently injured in civilian life. Most surgeons see relatively few fresh injuries of large blood vessels in their lifetime; however, any surgeon who is particularly interested in vascular problems will encounter an appalling number of disabling complications, amputations, and even deaths resulting from inadequate and improper treatment of vascular injuries.[1] Most of these catastrophes could be avoided if a few principles of management were better understood and more widely practiced. It is therefore appropriate to review, clarify, and augment these principles from time to time.

A blood vessel may be compressed, contused, partially severed, or completely severed. Compression usually results from angulation of a fractured bone, hemorrhage or swelling within an unyielding fascial compartment, or injudicious use of a tourniquet. It is easy to detect if one is aware of the danger and remembers to palpate the peripheral pulse after any injury. The unilateral absence of a peripheral pulse must be considered to be absolute evidence of arterial injury until proved otherwise. If the pressure is relieved before thrombosis occurs, permanent injury will be prevented. In the case of a fracture, gentle reduction usually suffices, and the return of an absent peripheral pulse after reduction of a fractured bone can be considered evidence that the artery had been compressed rather than seriously contused. Bleeding and swelling within a closed fascial space, such as the lateral compartment of the leg, may increase the pressure to the extent of compressing the remaining uninjured vessels and result in necrosis of all the enclosed tissue. This pressure should be relieved by immediate fasciotomy. Unfortunately, this procedure is usually not given sufficient consideration until after serious damage to soft tissues has taken place.

Contusion of blood vessels is more serious than compression. Contusion of a vein frequently leads to thrombosis, with the danger of subsequent embolization. Arterial contusion produces localized spasm, which not only reduces the volume of blood flow to the periphery but also encourages the formation of a thrombus, which may propagate and obstruct the collateral arteries.

Read at the Tenth Annual Meeting of the Central Surgical Association, March 6, 1953.

From the Department of Surgery of the College of Medicine, University of Cincinnati, and the Lucie Rawson Laboratory for Vascular Research of the Cincinnati General Hospital.

1. Herrmann, L. G., and Buchman, J. A.: Complications Resulting from Injuries to Major Arteries, Surgery **26**:59-66, 1949.

Errors in management of injuries to large blood vessels arise, in many instances, from failure of the physician to recognize the fact that there are at least two separate and distinct mechanisms for constricting peripheral blood vessels. Several important contributions have been made to this subject in recent years.[2] This concept is not widely appreciated, but it is of such fundamental importance that it merits special consideration at this time.

The first mechanism of vasoconstriction is the extrinsic control by the autonomic nervous system. There is ample evidence that the arterioles of human skin can constrict or relax after stimulation or paralysis of the sympathetic nerves or ganglia. Less evidence has been available, however, to indicate the part played by these nerves and ganglia in controlling the diameter of the arterioles of human muscle or the size of the named arteries of the body. Recently, light has been shed on this subject by the significant contributions of Kinmonth, Simeone, and Perlow.[2 a, b, c] Their observations suggest that the autonomic nervous system does not exert a direct influence on the aorta, carotid or iliac arteries, or the proximal portion of the femoral arteries but does influence the distal portion of the femoral arteries.

The second mechanism of vasoconstriction is the intrinsic ability of blood vessels to constrict when irritated. Constriction occurs independently of any extrinsic nervous influence, and it is just as complete in a denervated artery. The ability to constrict appears to be related to the amount of smooth muscle present in the wall of the vessel. For example, it is more difficult to demonstrate in the aorta or venae cavae, which have only a small amount of smooth muscle in their walls.[2a]

A third mechanism, which is probably, although not necessarily, identical with the foregoing, is the normal intrinsic tone of blood vessels. The diameter of a blood vessel expands or shrinks with changes in the volume of fluid within its lumen. Appreciation of this simple fact makes it clear that a shrunken artery distal to a point of occlusion is not necessarily indicative of the presence of "vasospasm." We do not speak of the collapsed gut distal to a point of obstruction as being in the state of "spasm," and yet a reduction of size of an artery distal to an occlusion is often thought to be due to reflex vasospasm. It is more reasonable to consider this reduction in size as a passive one due to the decrease in the volume and pressure of blood distal to the point of occlusion.

"Stupor artérielle," or "traumatic arterial vasospasm," is most probably due to direct trauma to an artery. It is a function of the intrinsic vasoconstricting mechanism and will persist as long as the stimulus continues. In fact, relaxation occurs some time after the stimulus has been removed.[2a] The classic example is constriction of the brachial artery following injuries about the elbow. The initial trauma

2. (*a*) Kinmonth, J. B.; Simeone, F. A., and Perlow, V.: Factors Affecting the Diameter of Large Arteries with Particular Reference to Traumatic Spasm, Surgery **26**:452-471, 1949. (*b*) Kinmonth, J. B., and Simeone, F. A.: Motor Innervation of Large Arteries with Particular Reference to the Lower Leg, Brit. J. Surg. **39**:333-335, 1952. (*c*) Kinmonth, J. B.: The Physiology and Relief of Traumatic Arterial Spasm, Brit. M. J. **1**:59-64, 1952. (*d*) Griffiths, D. L.: Volkmann's Ischaemic Contracture (Hunterian Lecture), Brit. J. Surg. **28**:239-260, 1940. (*e*) Cohen, S. M.: Traumatic Arterial Spasm, Lancet **1**:1-6, 1944. (*f*) Crystal, D. K.; Burgess, E., and Wangeman, C.: Thrombectomy in Volkmann's Contracture, New England J. Med. **247**:1015-1017, 1952. (*g*) Foisie, P. S.: Traumatic Arterial Vasospasm, ibid. **237**:295-302, 1947. (*h*) Pickering, G. W.: Vascular Spasm, Lancet **2**:845-850, 1951. (*i*) Gardner, C.: Traumatic Vasospasm and Its Complications, Am. J. Surg. **83**:468-470, 1952.

may be stretching of the artery over a displaced bone fragment, piercing of the artery by a spicule of bone, or hemorrhage into the wall of the artery, as demonstrated by Griffiths.[2d] If this spasm is not relieved, widespread thrombosis occurs and gives rise to typical ischemic necrosis of the muscles of the forearm. Neither periarterial neurectomy nor blockade of the autonomic nerves has been effective in releasing this type of arterial spasm.[2e,i] The artery should be exposed, extraluminal clots removed, spicules of bone searched for, and any fractured or dislocated bone reduced. If the wall of the artery is damaged or infiltrated with blood, the injured segment should be resected. If no evidence of injury is found, arteriotomy in search for intraluminal clots is indicated.[2f] Kinmonth [2c] has found papaverine and procaine to be the most effective agents for local use to relieve this spasm after the irritating agent has been eliminated.

There are several factors which determine the outcome of an injury that penetrates the lumen of a large blood vessel. Some of these need only to be mentioned; others merit detailed discussion. Obviously the size of the injured vessel and the extent and character of the penetrating wound are of paramount importance. Large lacerations of the aorta and venae cavae are seen but rarely in a living patient. A partially divided vessel is not able to constrict effectively and exsanguinating hemorrhage may occur even though the vessel is of small size. On the other hand, bleeding may be minimal if a large vessel is completely severed, because the divided ends are able to retract and constrict without interference. The resistance offered by the tissues to the outflow of blood is also an important determinant in the outcome of a fresh injury to a large blood vessel. A small laceration of the ascending aorta above the pericardial reflection usually causes fatal hemorrhage; however, ample time to treat the patient may be available if a laceration of the same size lies below the pericardial reflection. The clotting mechanism is an important factor in arresting hemorrhage after the rate and volume of blood flow through the opening has been reduced. Unfortunately, the problem does not end when a clot is formed, because secondary hemorrhage may occur after therapeutic elevation of the blood pressure or liquefaction of the clot. Furthermore, the clotting process may, in itself, lead to disaster by continuing unchecked. This process is particularly pernicious in both arteries and veins, with ischemic necrosis and arterial embolization occurring in the former and pulmonary embolization in the latter.

The lapse of time between injury of a large blood vessel and definitive treatment is a vitally important factor in determining the outcome. Within a few hours after the flow has been interrupted, the blood in the distal vessels begins to clot. If the clot remains localized, it may be possible to remove it by an early operative procedure; but if the clot extends and occludes the collateral arteries, irreversible changes are certain to take place.

The surgeon not only has the responsibility of minimizing the loss of time from the moment the patient comes under his care to definitive treatment but also the responsibility of teaching those who first see the injured patient to exercise all possible speed. Ideally, reparative operative procedures should be performed within six to eight hours; however, since it is impossible to state just when progressive thrombosis will begin in any given case, exploration should be carried out in all cases, even up to 24 hours after injury, unless evidence of ischemic necrosis or gangrene is present.

The first and cardinal principle of treatment of penetrating wounds of large blood vessels is that hemorrhage must be controlled. This requires emphasis because it is easy to become so engrossed in the general care of the patient, the treatment of shock, preparations for operation, and so on, that one overlooks the obvious fact that the patient's condition is deteriorating steadily as long as bleeding continues or at least as long as blood loss exceeds blood replacement. Bleeding must be stopped as soon as possible, even if this means immediate operation under unfavorable conditions. At the same time, however, one should avoid the use of methods that in themselves injure the patient or the extremity. A tourniquet occludes all the arterial inflow to an extremity. This occlusion increases the degree of ischemia in an already partially ischemic limb and also encourages thrombosis by bringing the flowing blood to a standstill. To be sure, a tourniquet may be life-saving after a very extensive injury, and one should not hesitate to endanger the viability of a limb to preserve the patient's life, but whenever it is possible to control hemorrhage by safer methods the use of a tourniquet should be avoided. Hemostatic clamps may cause further damage and should not be used in the case of fresh injuries to blood vessels unless they can be applied under direct vision to vessels in which restoration of continuity is unnecessary. If a clamp is used in a deep wound, a normal vessel or nerve may be inadvertently injured or the wall of the lacerated vessel may be crushed, the crushed wall making repair impossible.

A simple and safe method of controlling hemorrhage is the simultaneous use of local pressure and elevation of the part above the level of the heart. The finger is a blunt, soft, and safe instrument for compression of a vessel. The use of gauze makes it easier and more effective when the bleeding is from several vessels. If sufficient material is available, the wound can be packed and a smooth compression bandage that covers the entire extremity or the portion of the trunk distal to the wound may be applied. Care must be taken that the compression bandage does not act as a tourniquet. One should not be unduly concerned about the danger of introducing infection in a wound from which there is serious hemorrhage. Time is required for bacteria to multiply. All surgeons have seen heavily contaminated wounds heal without evidence of infection after adequate surgical cleansing and débridement. One should not hesitate to use a handkerchief or a soiled finger if necessary to stop severe bleeding.

Shock must be treated as soon as possible after the hemorrhage has been controlled or simultaneously with the effort to control hemorrhage if a surgical team is available. The need is for whole blood. While it is being obtained, an intravenous infusion should be begun, isotonic sodium chloride solution being used or a blood substitute if one is available. The patient can be placed in the head-down position within a few seconds' time in order to augment the flow of blood to the brain. In treating shock, however, it should be emphasized that it is neither necessary nor advisable to restore the blood pressure to the normal level before undertaking a surgical procedure. Increasing the pressure above the point necessary to sustain life merely increases the bleeding and may disrupt a soft clot. Recent experiences with hypotensive anesthesia [3] have shown it to be a valuable aid in the carrying

3. Griffiths, H. W. C., and Gillies, J.: Thoraco-Lumbar Splanchnicectomy and Sympathectomy: Anaesthetic Procedure, Anaesthesia **3**:134-146, 1948.

out of surgical operations that usually entail the loss of large amounts of blood. This technique is based upon the premise that the head of pressure necessary to drive the blood across the arterioles is greatly reduced if the arterioles are maintained in a state of maximum dilatation. The use of this method requires special training and skill on the part of the anesthetist, but the principle on which it is based is sound and should be recognized by all surgeons. A clear understanding of this concept will prompt the surgeon to take full advantage of the pendent position in augmenting blood flow to the cerebral centers and to avoid the use of peripheral vasoconstrictors to elevate blood pressure.

Before considering the technical aspects, it is well to have in mind the fact that restoration of continuity of a large blood vessel is not only unnecessary in many instances but actually involves a greater hazard for the patient than does proximal and distal ligation of the affected vessel. There is a tendency to think that the restoration of continuity by means of autografts or homografts is to be carried out whenever possible. This is not true, for, while there are instances in which it is essential to restore continuity by any means available, the use of such a method for restoration of continuity of a vessel that can be ligated safely exposes the limb to the needless danger of local, and possibly widespread, intravascular clotting of the blood.

The flow of blood is at a much slower velocity in the venous system than in the arterial tree, a fact which makes the danger of intravascular thrombosis considerably greater after repair of a vein than after repair of an artery. Furthermore, with the possible exception of the superior vena cava, the innominate artery, the inferior vena cava above the renal veins, and the superior and inferior mesenteric veins at their termination, any individual vein in the body may be ligated without endangering life and in the vast majority of instances without causing serious sequelae. Therefore it can be said that the use of a graft or prosthesis to repair an injured vein involves a greater risk than does a simple ligation. An exception to the rule of ligation by choice can be made in the case of a small rent in one of the vessels mentioned or of a vein of a large viscus that can be sutured without its lumen being constricted. But even suture is probably more hazardous than ligation in the case of large veins of the neck or extremities.

The task of setting specific rules is more difficult in the case of arterial injuries, because the existence of anomalies or pathologic changes in the arterial tree, as well as the extent of injury to the collateral arteries, is such an important factor in determining the outcome. Much of our information in this field comes from observations on patients with chronic occlusive arterial disease, and conclusions drawn from these observations do not necessarily apply to normal subjects. For example, in a patient with progressive arteriosclerosis of the lower extremity a popliteal aneurysm may develop, but the collateral arteries of his extremity enlarge as the occlusive process progresses in the distal arteries. If, by careful dissection, the popliteal artery is ligated proximally and distally and all the arteries entering the aneurysm are carefully sutured, it can be said that gangrene of the lower extremity will rarely, if ever, result from the procedure.[3a] On the other hand, if a bullet or knife severs the

3a. Linton, R. R.: The Arteriosclerotic Popliteal Aneurysm, Surgery **26**:41-58, 1949. Clear, J. J., and Herrmann, L. G.: Operative Treatment of Peripheral Aneurysms, A. M. A. Arch. Surg. **63**:452-457, 1951.

popliteal artery of a young man whose collateral arterial circulation is undeveloped, it is not possible to say that the popliteal artery can be ligated safely; furthermore, a clear distinction must be made between injuries to major arteries with or without injuries to the collateral vessels. It is improbable that permanent harm would result from ligation of a cleanly severed brachial artery; however, if this artery is severed by a wound of great violence, with widespread destruction of the collateral arteries, every effort must be made to restore its continuity. These difficulties seem to make the task insurmountable; nevertheless, it seems advisable to set down some general rules that may be useful as background knowledge in helping the physician to reach a decision in any specific instance.

The major arteries may be divided into three groups: those that can be ligated without complications in almost every instance; those that can be ligated without serious consequence under ideal conditions but not under less favorable conditions, and those in which ligation is always hazardous.

The first group includes all the arteries of the neck except the common and internal carotid, the arteries below the elbow and knee, and the left gastric, splenic, and internal iliac arteries. If a laceration of one of these arteries can be sutured without distorting the lumen excessively, so that a clot is likely to form, simple closure is indicated; however, the use of any type of graft or prosthesis to repair an injury to one of these arteries is unnecessary and entails a greater risk than does ligation.

The second group includes the internal carotid, subclavian, axillary, brachial, and popliteal arteries. It also includes the arteries of the abdominal viscera except the left gastric, splenic, and internal iliac arteries, which are in the first group, and the renal and hepatic arteries, which are in the third group. It is obvious that ligation is much safer for some arteries of this group than for others. The subclavian, axillary, and brachial arteries may be ligated in most instances unless there is extensive injury to the collateral arterial pathways. The intra-abdominal arteries of this group are not commonly injured, and when they are a great deal of help in making the decision as to whether or not they can be ligated can be obtained by observing the color changes in the viscus in which the arterial supply has been occluded temporarily. In the case of the internal carotid artery, much will depend upon the anatomy of the circle of Willis and the age and condition of the artery at the time of injury. The use of local anesthesia, to make questioning of the patient possible while the artery is occluded temporarily, is advisable. The most difficult decision is in the case of an injury to the popliteal artery. The small size of the artery makes the placement of a graft difficult and the danger of thrombosis at the site of repair very great. If the clot extends to the collateral arteries, the limb is lost. This situation may be the one instance in which an exception to the rule of immediate exploration can be made. If the bleeding stops spontaneously, the tissues are not under great tension, and the limb appears to be viable, it may be wise to treat the patient conservatively. If bleeding is severe, the wound of entry is small, and there has been little damage to the surrounding vessels, careful exposure of the artery with proximal and distal ligation is the treatment of choice. If the injury is one of great violence, and the collateral arteries are obviously damaged, one must attempt to restore continuity of the popliteal artery, because the incidence of gan-

grene in association with such injuries is high. DeBakey and Simeone [4] observed that gangrene followed 72.5% of war wounds of the popliteal artery.

The third group consists of the aorta, innominate, common carotid, renal, common and external iliac, and common and superficial femoral arteries. Gangrene does not always follow interruption of these arteries, but the incidence of gangrene is so high that repair is mandatory.

OPERATIVE TECHNIQUE

The operative technique need not be stereotyped, but a few principles should be observed. Sufficient exposure of the injured tissues should be obtained to make the procedure as easy as possible to perform. In general, an incision that lies in the same axis as the vessel to be exposed offers the best opportunity for adequate exposure. Proximal and distal control of the injured vessel must be obtained, as well as control of any collateral vessels entering the segment of artery or vein between the proximal and distal points of control. Surgeons who have a particular interest in this field will develop special instruments of their own liking, but these are not essential, and with a little improvising all the necessary equipment can be obtained in any operating suite. Umbilical tape and white shoelaces make excellent arterial compressors. Almost any type of soft-spring clamp may be used, as long as the wall of the vessel is not crushed. It is wise to use a cloth covering for all the usual types of clamp. The cloth not only helps avoid crushing of the vessel but also is less likely to slip than is metal or rubber. The Potts clamp should not be covered, of course, and it is excellent for use on arteries and larger veins; however, it may cut through thin-walled veins. Fine silk (No. 00000 or 000000) on swedged needles is readily available.

Many complicated techniques of suturing an artery have been devised, but simple methods are usually effective. The principles are to handle the artery gently, to excise adventitia near the line of suture, to use fine arterial silk on an atraumatic needle, to suture intima to intima with small enough bites so that the lumen is not significantly narrowed (a rough limit is 25% reduction in diameter), to be sure that the suture line will not be under tension at any time, and to eliminate any "dead space," so that the artery is not suspended in the wound. A solution of 100 mg. of heparin diluted in 10 cc. of isotonic sodium chloride solution can be injected into the lumen as it is closed. This procedure not only discourages local formation of blood clots during closure but also eliminates the air in the opened vessel.

Lacerated arteries may be closed longitudinally or transversely. Transverse closure has the advantage of increasing the diameter of the vessel at the point of suture and the disadvantage of angulating the artery, thus distorting the blood stream and giving rise to turbulence. If the laceration is irregular, division and primary anastomosis is the treatment of choice if it is possible to do them without creating tension at the suture line. Small gaps may be overcome by freeing the artery from its connective-tissue bed.

If the defect in the artery is too great to permit closure, continuity can be reestablished by means of a venous autograft. Such a graft is always available by

4. DeBakey, M. E., and Simeone, F. A.: Battle Injuries of the Arteries in World War II: Analysis of 2,471 Cases, Tr. South. S. A. **57**:65-110, 1946.

virtue of the fact that almost any large vein can be sacrificed without serious untoward effect. The concomitant or long saphenous veins are suitable and convenient to use. One must remember to reverse the vein if there is a valve present in the segment removed. The use of a venous autograft eliminates the difficulties of obtaining and storing arterial homografts and is probably the most practical method of handling acute arterial injuries. It is true that it is more likely to give rise to aneurysmal dilatation and to create turbulence in the blood stream, but it is a good method of treating an acute injury to a large blood vessel with minimum facilities.

In the case of a laceration of the aorta, innominate, or common iliac artery, the patient is likely to be in critical condition, and time may not be available to fashion and place a graft. A Vitallium or plastic tube may be lifesaving in this instance.

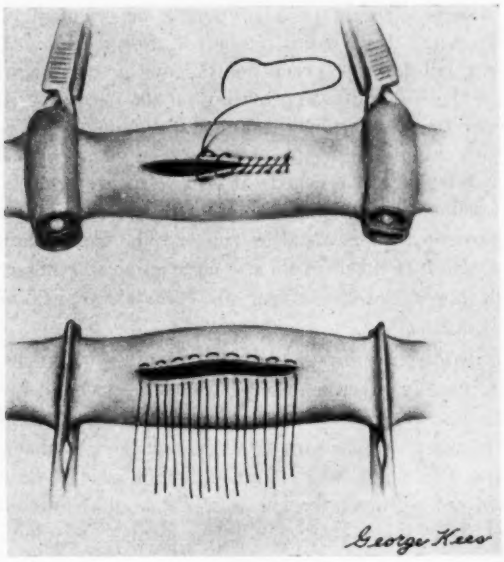

Fig. 1.—Top, longitudinal closure with a continuous everting suture. Bottom, longitudinal closure with interrupted mattress sutures.

Although a blood clot can be expected to form even while anticoagulants are being administered, time will have been gained during which the collateral circulation will improve. An elective operation can be performed in a day or two and the prosthesis be replaced by a venous autograft. It is in arteries the size of these that arterial homografts may prove to be of lasting benefit.

If an artery is to be ligated, nonabsorbable suture material should be used and the artery divided completely if it is not already completely severed. A transfixing ligature should be placed distal to the simple ligature.

Lumbar Sympathectomy.—One of the most frequent questions asked is whether or not a lumbar sympathectomy should be performed at the time of initial operation for treatment of a fresh arterial wound of the lower extremity or of the iliac artery. Unfortunately, a definite answer cannot be given at this time. Mention has been

made of the lack of evidence to support the concept of widespread "vasospasm" following injuries to large vessels. It is hazardous to conclude that "vasospasm" is present because an injured limb is cold and moist. This condition is a sign of sympathetic activity, which is present in any limb exposed to a cool atmosphere if the subject is in pain or is nervous or if the amount of blood which warms the limb is greatly reduced in volume. In our experience, the uninjured extremity is as cool and moist as the injured extremity unless it has been covered with more clothes and blankets than its fellow. This "spasm" can be relieved by covering the patient with a blanket and by using medicaments for the relief of pain.

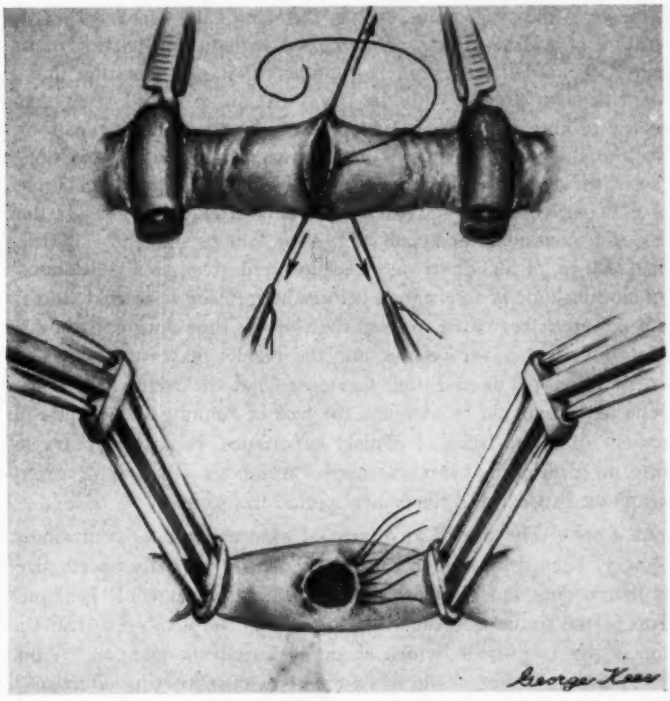

Fig. 2.—Top, end-to-end anastomosis with continuous suture. Note excision of adventitia near suture line and triangulation with stay sutures. Bottom, transverse closure with interrupted sutures.

Clinically, it appears that the nutrition of a limb with advanced ischemia improves slowly after lumbar sympathectomy and increases with the passage of time. If one is considering the long-term benefit to the arterial circulation of the limb, immediate sympathectomy is a reasonable procedure, provided the blood pressure of the patient is maintained; however, sufficient evidence is not available to enable one to say that it is helpful or necessary for prevention of gangrene following arterial injury.[4]

Postoperative Care.—One of the most serious pitfalls to avoid is a pronounced fall in blood pressure in patients in whom ischemia of the lower extremities is likely

to develop. Epinephrine-like vasoconstrictors do not help such patients, because they elevate the pressure by increasing the peripheral resistance in the arterioles, thus increasing the handicap of an ischemic limb. It is preferable to maintain blood pressure during and after surgery by the use of whole blood, given intravenously or intra-arterially, and to avoid vascoconstricting drugs. This therapy should eliminate the necessity of using "shock blocks." Elevation of a partially ischemic extremity because of postoperative hypotension may be the cause of some cases of "postsympathectomy" gangrene of the lower extremity.

Use of Anticoagulants.—Absolute indications for the use of anticoagulants cannot be set down at this time. Much will depend upon the individual preference and experience of the surgeon, as well as the size of the vessel and type of injury. If a laceration of a large artery can be closed without constriction of its diameter more than 25%, and the surgeon is confident that no adventitia and a minimal amount of silk is in contact with the blood stream, it would seem that the postoperative use of anticoagulants is unnecessary; however, after repair of a smaller artery, such as the popliteal, or one of the great veins or after insertion of a graft or prosthesis, the use of these agents is advisable. If hemostasis is complete, administration of heparin may be started immediately after operation. If there is considerable oozing, one must postpone its use for four to six hours; 200 mg. may be diluted in 1,000 cc. of 5% dextrose and water and given as a continuous infusion.[5] A control clotting time is determined before the infusion is started, and the number of drops a minute is regulated to keep the clotting time approximately three times the control. This test is very crude, and the results may vary widely even under optimum conditions; it is essential, therefore, that the technique be standardized. Ideally, one person should be assigned the task of running all the tests for an individual patient. On the basis of clinical experience, heparin appears to be more efficacious in preventing intravascular thrombosis than bishydroxycoumarin (Dicumarol); it is used until the critical period has passed.

General Care.—The use of any form of external heat is contraindicated. The limb is quickly burned by heat, because it is usually partially anesthetized and the poor circulation does not dissipate heat.[6] In addition, external heat increases the metabolism of the tissue and causes it to demand more oxygen than the deficient circulation is able to provide, which encourages ischemic necrosis.[7] Application of cold is also contraindicated. Cold has a direct vasoconstricting effect on blood vessels, even when they are denervated.[8] An environmental temperature of 90 to 92 F., as suggested by Starr,[9] appears to be optimal. This may be obtained by wrapping

5. Murray, G.: Anticoagulant Therapy with Heparin, Am. J. Med. **3**:468-471, 1947.

6. Starr, I., Jr.: On the Use of Heat, Desiccation and Oxygen in the Local Treatment of Advanced Peripheral Vascular Disease, Am. J. M. Sc. **187**:498-509, 1934.

7. Freeman, N. E.: Influence of Temperature on the Development of Gangrene in Peripheral Vascular Disease, Arch. Surg. **40**:326-333, 1940.

8. Buchanan, J. L.; Cranley, J. J., and Linton, R. R.: Observations on the Direct Effect of Cold on Blood Vessels in the Human Extremity and Its Relation to Peripheral Vascular Disease, Surgery **31**:62-73, 1952.

9. Starr, I.: Physiologic Considerations Concerned with the Pathogenesis and Treatment of Obstructive Vascular Disease (George E. Brown Memorial Lecture), Circulation **6**:643-660, 1952.

the extremity with cotton wadding to preserve body heat or by covering it with a tent, which also eliminates trauma by the sheets. Bed rest for 7 to 10 days after repair of a major vessel is advised.

SUMMARY

Injuries to large blood vessels are not common, but there is a high incidence of complications, which can be avoided in most instances by recognition of a few basic principles. Traumatic arterial vasospasm is most probably due to direct injury to an artery and cannot be relieved until the source of irritation is removed. This spasm is not mediated through the autonomic nervous system but is a function of a constricting mechanism inherent in the artery; treatment, therefore, must be based on direct surgical exposure of the artery in search of the offending agent.

The principles of definitive treatment of fresh injuries of large blood vessels are immediate control of hemorrhage by measures that are in themselves innocuous, treatment of shock without aiming to restore the level of blood pressure to normal before operation, early operative exposure of the injured vessel, discrimination between vessels that may be ligated by preference and those in which restoration of continuity is indicated, proximal and distal control of the vessel, avoidance of tension on the suture line or constriction of the vessel, closure of "dead space," and avoidance of postoperative hypotension.

TRANSLUMBAR AORTOGRAPHY AS A DIAGNOSTIC AID IN LOCALIZING ARTERIAL EMBOLI

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ACUTE ARTERIAL emboli carry a grave prognosis and commonly lead to gangrene of the extremity. These emboli usually originate in the left auricular appendage in persons with rheumatic disease of the mitral valve.

Aortography has not been extensively employed in the location of arterial occlusion from emboli.[1] However, its use as a diagnostic aid in localizing renal and suprarenal tumors has been of benefit to the urologist for over two decades.[2] Although the technique of this procedure is not new, its help in localizing the point of block in arterial disease has become popular only in the past few years.[3] In the treatment of patients with arteriosclerosis obliterans it is an extremely useful tool in determining the location and extent of the arteriosclerotic thrombi. Leriche and associates,[4] Wylie,[5] and others have described a technique of intimal stripping for treating these patients, in which they emphasize the cleavage plane which can be developed beneath the arteriosclerotic thrombus. Aortography is just as helpful in the localization of the acute embolus as it is in the diagnosis of obliterating arteriosclerosis.

Read at the Tenth Annual Meeting of the Central Surgical Association, Chicago, March 6, 1953.

From the Department of Surgery, the College of Medicine and the Surgical Service, the Medical Center, Ohio State University.

1. Donati, G. S.: In tema di arteriografia: Localizzazione di embolo dell' arteria iliaca primitiva mediante aortografia addominale retrograda; Embolectomia; Ripristino della pervietà della iliaca stessa, Atti Accad. fisiocrit. Siena (sez. med.-fis.) **18**:128-133, 1950.

2. dos Santos, R.; Lamas, A. C., and Caldas, J. P.: Artériographie des membres et de l'aorta abdominale, Paris, Masson and Cie, 1931; L'artériographie des membres l'aorte et de ses branches abdominales, Bull. et mém. Soc. nat. de chir. **55**:587-601 (May 4) 1929.

3. Allen, E. V., and Camp, J. D.: Arteriography: A Roentgenographic Study of the Peripheral Arteries of the Living Subject Following Their Injection with a Radiopaque Substance, J. A. M. A. **104**:618-624 (Feb. 23) 1935. Nelson, O. A.: Arteriography of Abdominal Organs by Aortic Injection: Preliminary Report, Surg., Gynec. & Obst. **74**:655-662 (March) 1942. Price, A. H., and Wagner, F. B., Jr.: Complete Occlusion of the Abdominal Aorta: Report of 2 Patients Diagnosed by Aortography, ibid. **84**:619-624 (April) 1947.

4. Leriche, R.; Beaconsfield, P., and Boëly, C.: Aortography: Its Interpretation and Value; A Report of 200 Cases, Surg., Gynec. & Obst. **94**:83-90 (Jan.) 1952.

5. Wylie, E. J.: Thromboendarterectomy for Arteriosclerotic Thrombosis of Major Arteries, Surgery **32**:275-292 (Aug.) 1952.

Aortography has a wider range of application than other procedures for arterial visualization. Femoral arteriography is simpler to perform and is of help in demonstration of the arteries of the thigh and leg. When the obstruction is in the common femoral artery or above, it is obviously useless.

Early surgical removal of arterial emboli in large arteries is usually indicated. There is a natural reluctance to operate, since the patient is a poor risk and the surgeon hopes that incomplete occlusion or an adequate collateral circulation will make operation unnecessary. Delay is costly, however, as viability may be temporarily maintained only to have gangrene soon appear. Even when the life of the limb is supported by collateral circulation, activity is sharply restricted, and claudication after minimal activity is common. Delay in early surgical treatment is brought about by uncertainty of diagnosis in the first few hours of an embolic occlusion, by indefinite localization of the block, and by hesitation to advise operation for the poor-risk patient without a clear-cut surgical indication.

Translumbar aortography is a safe procedure with few contraindications.[6] It is simple to perform and requires only a few minutes. In the management of an arterial embolus, hours may be saved if there is any question of diagnosis. There is no need to delay operation to perform aortography. Anesthesia is started and aortography is done while the operating room is being set up for surgery. If operation is indicated, anesthesia is continued and embolectomy is accomplished. The incision can be accurately placed for precise exposure of the embolus, a minimum of operating time thus being required. Translumbar aortography is of aid in the management of peripheral arterial embolus because it confirms the diagnosis without delay and accurately localizes the block.

TECHNIC

The two-needle technic as described by Wylie is used. The injection is carried out rapidly, and the first x-ray is taken when a few cubic centimeters of solution is left in each syringe. Two subsequent exposures are taken as rapidly as the cassettes can be changed. Each change takes about 5 seconds. The needles are left in place until the wet films are read. If for any reason other x-rays are needed, an additional injection of 70% iodopyracet (Diodrast) not to exceed a total of 200 cc. may be made. Extravasation of the opaque material occasionally occurs and causes transitory back pain. No more serious effects have been observed, and by x-ray the iodopyracet has been found to be absorbed and excreted within 12 hours.

REPORT OF CASES

CASE 1.—M. H., a 21-year-old white woman, was admitted to the Ohio State University Medical Center Hospital on Sept. 17, 1952 with a chief complaint of shortness of breath and an enlarged heart. The patient had had an ache in her left arm for about two months, became dyspneic prior to admission, and was referred to the hospital for investigation. Physical examination revealed no abnormalities. Fluoroscopic and film studies of the chest showed a cystic mass in the right lower hemithorax.

6. Wagner, F. B., Jr.; Price, A. H., and Swenson, P. C.: Abdominal Arteriography: Technique and Diagnostic Application, Am. J. Roentgenol. **58**:591-598 (Nov.) 1947. Wagner, F. B., Jr., and Price, A. H.: Fatality After Abdominal Arteriography: Prevention by New Modification of Technique, Surgery **27**:621-626 (April) 1950.

Hospital Course.—A complete work-up failed to reveal a definite diagnosis of the lesion in the right chest close to the heart. The patient was transferred to the surgical service on Oct. 1, and right exploratory thoracotomy was performed. The tumor was clinically thought to be a sarcoma, and biopsy revealed a fibrosarcoma. The postoperative course was uneventful for five days. At 8 p. m. on Oct. 10, the sixth postoperative day, the patient complained of pain in the left leg, and the left leg was colder than the right. Sympathetic block was performed with injection of 1% procaine hydrochloride; the patient's pain was relieved somewhat, but no pulsation was demonstrable in or below the femoral artery and the left extremity was extremely cold. Oscillometric readings showed no pulsation. Pulsations on the right were diminished from

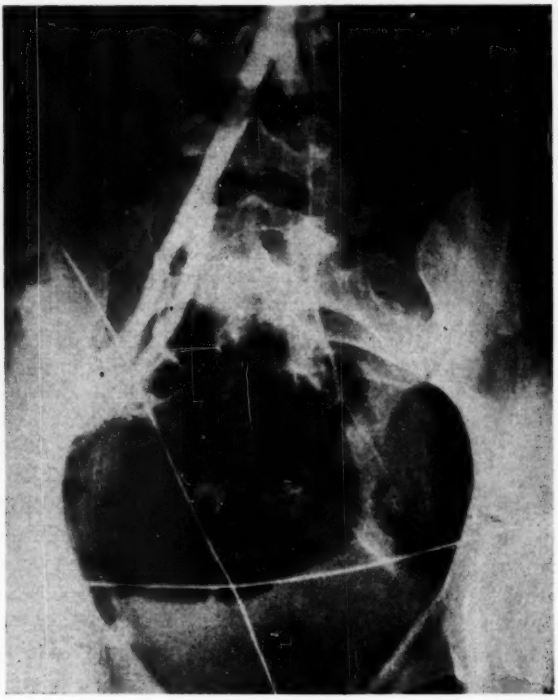

Fig. 1 (Case 1).—Aortogram showing block in left common iliac artery.

normal. At 10 p. m. an aortogram was made and revealed a block in the left iliac artery. At 1 a. m. on Oct. 11 the patient was taken to the operating room, and through a left low paramedian incision the left iliac artery was exposed. The embolus could be easily felt in the left iliac artery, extending down into the femoral. An incision was made in the long axis of the vessel, and a large clot was removed. Unfortunately the lower ends were extremely friable; the clot fragmented on removal, and irrigation with heparin solution could not dislodge the lower ends of the clot. The artery was closed with an over-and-over running suture of No. 000000 arterial silk. The patient was given trypsin intravenously in an attempt to dissolve the clot remaining after operation, but the left leg did not respond; it continued to be cold and pale, and on the fourth day after embolectomy the left foot became demarcated with an area of gangrene beginning 2 in. (6.1 cm.) below the left knee. On Oct. 15 a left-leg amputation was performed in the low mid-thigh, and the further course was uneventful.

Aortography in this case was the only practical means of revealing the site of block by direct visualization. In spite of the unhappy end-result from this embolism, the aortogram was of help in management. The acute occlusion of the left iliac artery was demonstrated (Fig. 1).

CASE 2.—M. C. (No. 504518A), a 55-year-old white woman, entered the Ohio State University Medical Center Hospital seven days after a left inguinal herniorrhaphy done at another hospital. The immediate postoperative course was uneventful until the fifth postoperative day, when, after a short walk in the hospital corridor, the patient was seized with a sudden sharp pain in the right leg followed by pallor and coldness of this extremity. Because the patient was known to have mitral stenosis, it was assumed that an arterial embolus had occurred in spite of the fact that there was no history of auricular fibrillation.

Subsequent to the acute episode, bed rest was prescribed. Vasodilation with intravenous injection of tetraethylammonium (Etamon) chloride was employed. Twenty-four hours later (one day prior to admission) essentially the same symptoms occurred in the left leg, followed by pallor and coldness of the limb. No frank cyanosis was ever apparent in either leg, although both legs were pale and cool. The pain and coldness improved slightly within one hour after onset, but no further improvement occurred. The pain did not completely subside, and the patient was transferred to University Hospital for further treatment.

Past History.—In 1950 the patient had a left lower lobectomy for bronchiectasis. She was known to have had mitral stenosis for 15 years without ever having fibrillation or decompensation.

Physical Examination.—Blood pressure was 126/78, and pulse rate 80. Her temperature and respirations were within normal limits. The positive physical findings included a heart that was enlarged to the left midaxillary line, with a loud, harsh, crescendo type of apical systolic and presystolic murmur. The operative scar on the left chest was well healed. Dullness, consistent with postoperative pleural thickening, was found in this area. Breath sounds were normal throughout both lung fields. Femoral pulses were palpable bilaterally, but all pulses distal to this point were absent. Oscillometeric readings showed diminished to absent pulsations in both thighs and calves. The skin temperature was lowered in the left leg, and although the previously mentioned pallor was present, there was no cyanosis.

Hospital Course.—On admission to the hospital, a left lumbar paravertebral sympathetic block was performed with 2% procaine hydrochloride. This immediately relieved the pain and improved the circulation, so that the skin temperature, although somewhat low, was the same on the two sides. An aortogram, made 18 hours after admission (Fig. 2), showed filling defects bilaterally, each located just distal to the profunda branch of the femoral artery. Delayed retrograde filling of both femoral arteries was also noted in the films taken five seconds after the initial exposure (Fig. 3). The patient was allowed to be ambulatory in her room but could walk only a few steps without claudication in both calves.

Because the collateral circulation was obviously sufficient to support life in the limb, but since function, as measured by the claudication time, was markedly restricted, it was felt that delayed embolectomy was feasible. The first clot was removed from the right femoral artery four days after admission, and the second clot was removed from the left femoral artery four days later. The two operations were technically performed in a similar manner.

The incision was made directly over the artery, and the artery was easily exposed and found to be pulseless just below the profunda. The retrograde filling was visible on x-ray examination, and by palpation the femoral arterial wall was normal. After isolation of the field by bulldog clamps, a linear incision was made over the clot, and the clot was removed. The occlusion at the origin of the superficial femoral artery was complete on both sides, but the clots were easily removed, and the underlying intima was only slightly roughened and edematous. Arterial closure was accomplished with an over-and-over suture of No. 000000 arterial silk.

Postoperative anticoagulant therapy was started with long-acting heparin given twice daily and its use continued for four days. The clotting time for this period was maintained at between 20 and 30 minutes. Within four hours after operation on each side, peripheral pulses returned,

and oscillometric readings were normal by the second postoperative day. The patient was allowed to be ambulatory in her room and had no claudication. She was discharged on the eighth day after the second operation free of symptoms referable to the lower extremities. She has remained well, with normal circulation in both legs.

Clinical localization of the bilateral femoral block in this case could be accurately determined. The aortogram confirmed this localization, and by demonstrating reflux filling of the superficial femoral artery below the embolic occlusion indicated that late femoral embolectomy was feasible.

Fig. 2 (Case 2).—Aortogram 1, showing occlusion of superficial femoral artery on both sides.

CASE 3.—B. S., a 56-year-old white woman, was admitted to the Miami Valley Hospital, Dayton, Ohio, with a chief complaint of severe bilateral pain and coldness of the lower extremities. Frank cyanosis and demarcation at the midthigh were evident on admission.

Past History.—The patient was known to have hypertension; she had not had demonstrable auricular fibrillation but had had multiple episodes of cardiac failure.

Examination.—The patient was a moderately obese white woman in moderate cardiac failure, with frank cyanosis and gangrene beginning at the left midthigh. The right leg was cold and pale, but was not cyanotic or gangrenous. Femoral pulses were imperceptible bilaterally, and oscillometric readings in the lower legs gave negative results.

Hospital Course.—Aortography revealed the site of obstruction in the lower aorta (Fig. 4). Direct attack on the aortic embolus was obviously not feasible. An amputation was performed high in the left thigh, but the patient did not respond and died of uremia six weeks postoperatively.

In this case aortography was helpful only in the premortem diagnosis.

CASE 4.—B. K., a 53-year-old white man, entered White Cross Hospital, Columbus, Ohio, on Aug. 9, 1952, complaining of numbness and weakness of the lower extremities. The patient had been under treatment for auricular fibrillation for three years. He was known to have poor

Fig. 3 (Case 2).—Aortogram 2 (taken five seconds after that shown in Figure 2), showing reflux filling of superficial femoral arteries below site of block.

arterial circulation in his legs and head and complained of claudication after a few steps of one year's duration. The patient was well and at work until 3 p. m. of the day of admission, when he suffered a sudden attack of syncope followed by numbness, coldness, and pallor of the legs. He began to perspire profusely and was taken home. His physician was called. The patient was given morphine for pain and sent to the hospital by ambulance.

Past History.—The patient had had rheumatic fever with chorea at 12 and frequent episodes of shortness of breath thereafter. He had been treated with digitalis for heart failure and had been in auricular fibrillation for four years. He had had intermittent claudication for the past year and had been treated for poor circulation in the legs. The cardiologist who had been treating him reported that femoral pulsations had previously been diminished and that oscillometric readings showed pulsations to be absent in the thighs and legs.

Examination.—Blood pressure was 210/110. Temperature was 98.4 F. Pulse rate was 92 and grossly irregular. Respirations were 28. The patient was a well-developed and well-nourished white man who was short of breath. The cervical veins were distended, and the lungs showed basal râles. The heart was enlarged, and the rhythm was grossly irregular. The legs were pale, with diminished sensation and no pulsations. Reflexes were hypoactive. Oscillometric readings showed no pulsations in the lower extremities.

Hospital Course.—A diagnosis of saddle embolus was made and was confirmed by aortogram. The patient was taken to the operating room, and while he was under general anesthesia the aorta was exposed through a left rectus incision centered at the umbilicus. A typical Y-shaped embolus was found at the bifurcation and easily removed. The patient was cyanotic

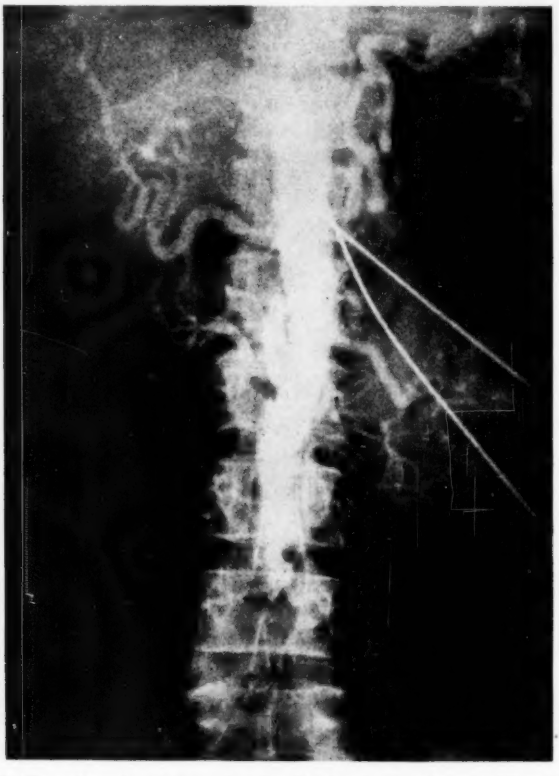

Fig. 4 (Case 3).—Aortogram showing block of aorta from saddle embolus.

during the operation but responded well during the first 12 postoperative hours. His legs resumed normal color and warmth, but oscillometric readings still showed diminished pulsations. Twenty-four hours postoperatively the patient showed signs of increasing congestive failure. Pulmonary edema was progressively more severe, and he died on the second postoperative day. Postmortem examination was done. The cause of death was congestive heart failure.

This patient had findings that were characteristic of a saddle embolus to the aorta, but because of the previous record of severely diminished arterial circulation in the legs, the possibility of a bilateral femoral thrombotic obstruction had to be considered. The aortogram localized the block in the aorta. Surgical removal of

the embolus was attempted in this extremely poor-risk patient with the knowledge that fatal termination of the illness was probable unless successful embolectomy could be accomplished.

CASE 5.—R. N., a 46-year-old white man, was admitted to the Ohio State University Medical Center Hospital for the first time because of excruciating pain in both lower extremities. The patient was apparently well until 30 minutes prior to admission, when, while standing in a drugstore, he was seized with sudden, continuous, and severe pain in the lower abdomen and both lower extremities and collapsed. He was brought to the hospital by ambulance.

Past History.—The patient had been treated for cardiac disease for 20 years. He had had two episodes of acute rheumatic fever and had suffered occasional dyspnea on exertion, with a markedly decreased exercise tolerance.

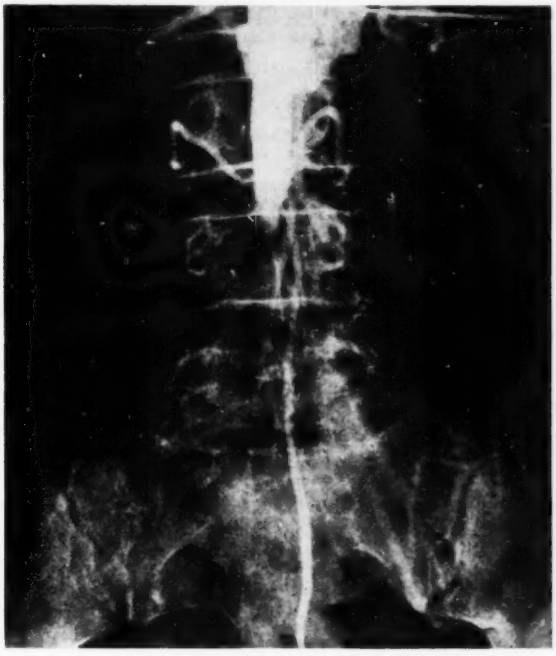

Fig. 5 (Case 5).—Aortogram showing block of aorta from saddle embolus.

The patient was in shock, the blood pressure was 85/40, and the pulse was impalpable in all extremities. All extremities were cold and moist; the lower extremities were extremely pale. An aortic pulse could be felt above the umbilicus but could not be felt below the umbilicus. Femoral pulses were absent, and oscillometric readings showed no pulsations in the lower legs.

Hospital Course.—The patient was given morphine intravenously, obtained some relief from his pain, and within an hour after admission the quality of his heart sounds improved, his blood pressure stabilized at 120, and his general condition was improved. Pulses developed in the upper extremities but not in the lower extremities. Four hours after onset of symptoms aortograms were obtained which showed a complete occlusion of the aorta just above its bifurcation, thereby confirming the diagnosis of saddle embolus (Fig. 5). The patient was taken directly to the operating room and a saddle embolus removed from the bifurcation of the aorta.

Technically the operation was performed through a left midrectus incision. The aorta was mobilized from just below the renal vessels past the bifurcation to the hypogastric vessels

bilaterally. The clot was palpable in both iliac vessels and no pulsations were discernible beyond this point. The aorta was clamped below the renal arteries with a Blalock clamp, and all tributaries were occluded with bulldog clamps. Distal clamps were applied first to diminish the chance of dislodging the clot during manipulation. A 5-cm. linear incision was made in the aorta just above the bifurcation, and the clot was removed. It was loosely attached and was removed in one piece. Slight retrograde bleeding was obtained distally, and temporary release of the aortic clamp gave a free flow of blood. The incision in the aorta was closed with an over-and-over suture of No. 000000 arterial silk.

Postoperatively, pulsations returned to the lower extremities in one hour, and oscillometric readings were normal by the second postoperative day. Long-acting heparin was employed in this case (200 mg. twice daily) in amount sufficient to maintain the clotting time at between 20 and 30 minutes. This therapy was discontinued after 48 hours.

The patient was discharged on the 14th postoperative day to the care of his family physician and has had normal circulation in his lower extremities. He has since had a mitral commissurotomy, with improvement in the cardiac symptoms and in exercise tolerance.

This patient was comparatively young, was a good surgical risk, and was seen soon after his saddle embolus. These were the most important factors in the successful result. It was felt that operation was performed earlier because of the definite diagnosis given by the aortogram.

Of minor interest is the placing of the incision for exposure of the aorta. There is a tendency, at least on our part, to place the incision too low. The abdominal aorta is essentially an upper abdominal organ, and a vertical incision centered slightly above the umbilicus gives excellent exposure.

CONCLUSIONS

1. Translumbar aortography is practical and safe.

2. It is of aid in the management of arterial emboli, because it establishes the diagnosis without delay and accurately localizes the site of occlusion.

DISCUSSION

ON PAPERS BY DRS. HERRMANN AND CRANLEY AND DRS. LOVINGOOD AND PATTON

DR. WILLIAM D. HOLDEN, Cleveland: I should like to make a few comments about the paper that Dr. Cranley gave.

There was one particular point concerning segmental arteriospasm, sometimes referred to as intrinsic arteriospasm or myogenic spasm, that I think is extremely important. He referred to some of the experimental work that has been done by Kinmonth, and I should like to call attention to some additional work that he has performed.

This work was mentioned in connection with one of Dr. Cranley's slides—the spraying of the adventitia of an artery that has been subjected to intrinsic myogenic arteriospasm with procaine or papaverine. In a high percentage of experimental animals, Kinmonth has been able to relieve this intrinsic type of arteriospasm by spraying the adventitia with papaverine.

I think this is extremely important because patients who have myogenic arteriospasm are unusually difficult to manage. I should much prefer to manage a patient with acute thrombosis within the artery than one with intrinsic arteriospasm, because at present many of those patients finally have an amputation of the extremity. Up to the present there is no means whatever of successfully, directly, and intentionally relieving such arteriospasm.

Now, if papaverine sprayed upon the adventitia in animals is as effective as Kinmonth has demonstrated, it becomes important for surgeons to find out whether the same is true in human beings.

There is a tremendous species difference so far as the responses of the peripheral arterial tree is concerned to various types of trauma. I do not know whether this is going to be true

in human beings or not. I have had one occasion to spray papaverine upon a major artery that was in a state of intrinsic spasm, and it had no beneficial effect whatever. Even over a considerable period of time one does not see many of these patients.

I think it becomes important for all of us to realize that, experimentally, this successful therapeutic procedure has been demonstrated, and we must find out whether it is going to be useful in human beings or not.

It is of very little value to inject the papaverine into the lumen of the vessel. I have done that on many occasions and have never been able to demonstrate more than a very transient improvement in the circulation or a transient dilatation of the artery. I have never seen any permanent benefit resulting from the intra-arterial injection of papaverine.

Dr. Harris B. Shumacker, Jr., Indianapolis: I am sorry to find myself somewhat in disagreement with the conclusions drawn from the very beautifully presented paper by Drs. Lovingood and Patton.

During the past 15 years or so, my associates and I have treated a considerable number of patients with peripheral arterial embolism involving the aorta and the brachial, the iliac, the femoral, and the popliteal arteries. During this time there have been two patients in whom the embolus was not found at exploration, presumably having been dislodged and passed distally, either immediately before or during the exploration. These two patients survived without gangrene. In all other instances, the embolus has been found at the site of localization arrived at from clinical observation alone. The criteria upon which localization is based include the lowest level of pulse palpable, the level of discoloration, coldness, hypesthesia or anesthesia, and motor paralysis. Those observations are well known and therefore permit one to localize the level of obstruction with great accuracy.

As a consequence, I feel that aortography is not needed in the accurate localization of peripheral arterial emboli. Aortography carries with it a very minimal risk, to be sure, but some risk. It can be performed rapidly, but it does dissipate some valuable time, and since the localization can be made so well without it, I do not believe it should be employed as a routine.

Dr. Charles G. Johnston, Detroit: I am very happy to discuss Drs. Cranley and Herrmann's paper because they have presented some very important fundamental concepts, some of which we have had a tendency to forget.

I am reminded that a few years ago the question was raised as to whether one had to carry out the usual surgical cleansing techniques now that we had antibiotics. Dr. Cranley has brought up the question that seems to have been forgotten and that is the question of the ligation of vessels—those which may or may not be ligated. I am sure that the medical students of today do not learn the sites of election that we have had to learn previously. This is still an important problem. All injured vessels cannot be repaired, and some must be ligated.

I have taken the stand and publicly stated that I think whenever a vessel can be repaired it should be. It is a matter of conservation of important structures, and I think vessels are important.

In relation to the teaching of residents, we have taken the viewpoint that even the smaller arteries ought to be sutured, because if they can suture the small vessels, they will not have trouble with the larger vessels. I think one of the problems in relation to saving those patients who have arterial injuries is that surgeons are afraid to attempt suture of any arteries. It is amazing, but after suturing one or two arteries, especially the small ones, there is usually little fear because the problem is not so difficult.

I should like to make one comment about segmental arteriospasm. Dr. Cranley did not stress this too much, and we probably should not discuss it. However, I have not seen a true case of segmental arteriospasm in a human being. I feel that in persons suspected of having arteriospasm, if their arteries are explored, other problems will be found in that area.

We have had three patients in whom I suspected and was rather sure we were going to find arteriospasm as a sole cause. Injuries about the vessel or to the vessel were found in all three. I feel it is important that exploration be done in all these cases. I shall keep on doing such explorations, expecting some day to find a true case of arteriospasm, because such cases have been reported, and I feel therefore that they must exist; I just have not encountered any, and there has always been some other explanation for occlusion in my cases.

I should like to second what Dr. Shumacker said—and extend it a little—about the aortograph in relation to the embolus.

Usually the site of an embolus can be easily determined. In most instances, when the blood pressure is still good, one can almost spot the very point where the embolus begins because of the increased pulsation above the occlusion, as compared with the other side, and lower down, because of the complete absence of any pulse. The arteriogram delineates the uppermost portion of the occlusion. This is not so important, since if one can remove the lowermost portion of the clot the uppermost portion will take care of itself.

Segmental arterial spasm is not frequently encountered, but when it does occur it usually results in loss, or permanent deformity, of the limb (Volkmann's contracture). The point to be emphasized is that this type of spasm is not produced by reflex vasoconstriction but is the result of a direct injury to the artery. One should not expect, therefore, to relieve this spasm by medicinal agents or by anesthetization of the regional sympathetic ganglia. The artery must be explored without delay, the offending agent eliminated, and only then a relaxing agent, such as papaverine, applied locally.

DR. JOHN J. CRANLEY, Cincinnati: I should like to thank Dr. Holden for calling attention to the further work of Kinmonth, which we omitted because of the time limitation.

Kinmonth found papaverine to be the most effective of the agents he used to relax intrinsic spasm. Procaine hydrochloride, 2%, caffeine, and warm saline also brought about relaxation of the arteries, but this relaxation did not persist as long as it did when papaverine sulfate was used. To date, then, we will have to conclude that it is the agent of choice.

I should like to thank Dr. Johnston, too, for his comments. If small vessels are to be sutured for training purposes, we would have no objection in the case of arteries. However, we would not advocate the suture or anastomosis of small veins for any purpose because of the danger of thrombosis, with subsequent propagation of the clot.

CARCINOMA OF THE THYROID

A Clinicopathologic Study

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IN A REVIEW of 1,928 consecutive thyroidectomies performed at the University of Michigan Hospital during the 15-year period from 1935 to 1950, 145 cases of malignant disease of the thyroid were found. Based on pathologic and clinical studies, groups of patients with early and with advanced carcinoma were separated for comparison, and special attention was devoted to the age of the patient, histopathology of the tumor, and cervical lymph node metastases as prognostic signs. A statement regarding therapy is included in this report.

Inasmuch as the morphologic criteria required for the diagnosis of cancer of the thyroid gland have been controversial, it should be stated that the pathologists at the University of Michigan Hospital made the diagnosis in these cases according to the criteria utilized in recognizing cancer in other tissues, namely, infiltrative growth, cellular dedifferentiation, nuclear hyperchromatism, mitotic figures, and atypical cells. Not all these features were necessarily present in each instance, but all were considered in the final diagnosis.

Although the series reviewed included the patients with operable as well as those with inoperable carcinoma, patients in a hopelessly terminal state (carcinoma too advanced for consideration of operation), patients who refused operation, those who had only a biopsy, and those who were referred for consultation only were not included.

MATERIAL

Of the 145 patients with malignant disease of the thyroid gland, 6 had metastatic involvement from primary sites in other organs and will be discussed separately. The 139 patients with primary malignant disease of the thyroid gland represented a 7.21% incidence of cancer in the total series of thyroidectomies. This incidence is higher than that usually reported in the literature [1] but may be attributed to the histologic diagnosis of early carcinoma (Table 1).

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1. Cole, W. H.; Slaughter, D. P., and Majarakis, J. D.: Carcinoma of the Thyroid Gland, Surg., Gynec. & Obst. **89**:349-356, 1949. Ward, R.: Symposium on Surgical Lesions of the Thyroid: Malignant Goiter, Surgery **16**:783-803, 1944.

Slightly more than one-half of the thyroid carcinomas diagnosed in the 15-year period were considered as early carcinomas. None of the 68 patients had clinical manifestation of local or distant metastases or evidence of blood or lymphatic vascular invasion in the sections examined. Two groups with early carcinoma were established on the basis of whether capsular involvement of the adenoma was demonstrable or not.

Group 1 consisted of 37 patients and represented early carcinoma within an adenoma. The neoplasm was confined within the capsule of the adenoma, but the proliferative changes were sufficiently atypical to warrant a diagnosis of early carcinoma. The neoplasm was probably completely removed by thyroidectomy, and the finding of carcinoma did not adversely influence the prognosis.

Group 2 consisted of 31 patients and included examples of carcinoma in an adenoma with early infiltration of the capsule of the adenoma of origin. These carcinomas were thought to have been completely removed but carried a "somewhat guarded" prognosis.

TABLE 1.—*Incidence of Cancer of the Thyroid*

	No.	%
Thyroidectomies performed	1,928	.....
Glands with nonmalignant disease	1,789	92.79
Glands with malignant disease	139	7.21
Carcinomas	134	6.95
Group 1	37	1.92
Group 2	31	1.61
Group 3	66	3.42
Sarcomas	5	0.26

Our third group (Group 3) combined the patients with advanced carcinomas. These 66 patients, representing 3.42% of the entire series of thyroidectomies, exhibited widespread infiltration of the thyroid gland proper or of adjacent tissues or had regional lymph node and/or distant metastases.

Five sarcomas of the thyroid were encountered. Each of the sarcomas was diagnosed microscopically as spindle-cell in type. It is appreciated that most examples of "sarcoma" of the thyroid are poorly differentiated carcinoma, but other histologic features strongly supported the diagnosis of sarcoma in these cases.

INCIDENCE

Other authors have agreed[2] that in most instances the thyroid "nodule," or adenoma, is the site of origin of carcinoma of the thyroid. Table 2 summarizes the incidence of carcinoma as found in the various types of goiter in our series. In three of our patients the carcinomas appeared to arise in diffusely enlarged glands. These glands each contained far-advanced neoplasm with widespread local infiltration, and it is possible that adenomas were destroyed by the extensive infiltrative process.

2. Coller, F. A.: Adenoma and Cancer of the Thyroid: Study of Their Relation in 90 Epithelial Neoplasms of the Thyroid, J. A. M. A. **92**:457-462, 1929. Ward, R.: Malignant Goiter: Lessons to Be Learned from a 20-Year Follow-Up, West. J. Surg. **55**:383-388, 1947. Cole.[1] Ward, R.: Symposium on Surgical Lesions of the Thyroid: Malignant Goiter, Surgery **16**:783-803, 1944.

Of the 1,455 nodular goiters, 131, or approximately 9%, contained carcinoma. The glands with a single nodule showed a much higher incidence of carcinoma (24%) than did glands with multiple nodules (7.54%). There was no significant correlation between the occurrence of carcinoma and the size of the nodule in either group.

Separation of the patients into those with single and those with multiple nodules was accomplished by gross examination of the gland after thyroidectomy and not by clinical palpation alone. Lange and MacLean [3] reported the error which may

TABLE 2.—*Incidence of Carcinoma and Type of Goiter*

Type of Goiter	No. of Thyroid-ectomies	Carcinoma	% of Carcinoma
Diffuse	473	3	0.63
Nodular	1,455	131	9.00
Multiple nodules	1,327	100	7.54
Single nodule	128	31	24.30

TABLE 3.—*Sex Incidence of Thyroid Cancer*

Sex	No. of Thyroid-ectomies	No. of Cancers	%
Female	1,520	101	6.64
Male	408	38	9.31
Total	1,928	139	7.21

TABLE 4.—*Age Distribution of Thyroid Cancer*

Age, Yr.	Females	Males	Total
0-10	0	1	1
11-20	5	5	10
21-30	11	7	18
31-40	20	7	27
41-50	25	4	29
51-60	20	4	24
61-70	16	6	22
71-80	4	3	7
81-90	0	1	1
Total	101	38	139

result from estimating the number of nodules in a thyroid gland by clinical palpation. They reported that of 159 glands which were thought clinically to contain solitary nodules, examination after thyroidectomy revealed only 31 with solitary nodules, 2 with no nodules, and the remaining 126 with multiple nodules.

The statistics of the sex incidence of thyroid cancer include the five cases of sarcoma (Table 3). Cancer occurred in the thyroid glands of 101 females and 38 males. Although it appeared from percentages that males with goiter showed a greater incidence of carcinoma (9.31% to 6.65%), thyroid carcinoma and thyroid disease in general were more common in females.

3. Lange, H. J., and MacLean, K. F.: Malignant Neoplasms of the Thyroid, Surgery **26**:862-886, 1949.

The age incidence of carcinoma of the thyroid is summarized in Table 4. A fairly even distribution of cases appeared to occur from 20 to 70 years. Forty per cent of the patients were less than 40 years of age. Eleven patients were under 20, the youngest being a 3-year-old boy, who was the youngest patient with carcinoma of the thyroid we found reported on in the literature.

Hyperthyroidism was of little importance in the differential diagnosis of malignant goiter. Symptoms of hyperthyroidism, including an elevated basal metabolic rate, were present in approximately 25% of the patients in the series.

PATHOLOGIC ASPECTS AND CLINICAL FOLLOW-UP

Early Carcinoma.—Inasmuch as only a small area of an adenoma is examined in the routine pathologic sampling process, additional sections occasionally disclose areas of invasion by suspicious adenomas. Such nodules must be sampled adequately before the diagnosis of carcinoma can be confirmed or rejected histologically. Firm, opaque, yellow to grayish-white areas in a nodule (or gland) should be examined as possibly malignant.

The cells in early thyroid carcinomas are, for the most part, well differentiated, 65% of them being adenocarcinomatous, 20% papilliferous, and 12% hyper-

TABLE 5.—*Survival of Patients with Thyroid Cancer, One Hundred Per Cent Follow-Up*

Group	No. of Patients	1-5 Yr. Survival	5-10 Yr. Survival	10-15 Yr. Survival	Over 15 Yr. Survival
Early carcinoma *	68	15	19	17	8
Advanced papilliferous carcinoma †	23	10	7	2	0
Nonpapilliferous carcinoma †	43	11	5	1	0
Sarcoma	5	0	0	0	0

* Grades 1 and 2.
† Grade 3.

nephroid. The remaining 3% are mixtures of these cell types. The acidophilic, so-called Hürthle-cell, change was noted in two cases in Group 2, in one of which the carcinoma was predominantly well-differentiated adenocarcinoma. Of the two recurrences in Group 2, one was in a gland which showed a Hürthle-cell adenocarcinoma; the other was in a gland with papilliferous adenocarcinoma. That none of the more anaplastic cell types were noted in this group suggests the possibility that anaplasia develops only after definite invasive and metastasizing qualities are present in the growth.

In several instances, multiple cellular adenomas were found, more than one of which showed carcinomatous change. Some examples of carcinoma were noted in and around calcified adenomas but were infrequent in this material. The so-called fetal and embryonal adenomas were distinguished and were not included unless malignant changes were present.

Of the 68 patients with early carcinoma (Groups 1 and 2), only 9 have died, and in no instance was death attributed to neoplasm of the thyroid gland. Two patients in Group 2 have had recurrences, one 4 years and the other 14 years after thyroidectomy. The recurrent growths were excised and radiation administered, and the patients were living, apparently free of neoplasm at the time of follow-up, one and three years later, respectively. Of the patients, 44 have survived a 5-year period; 17 of the 44 have lived more than 10 years, and 8 others have lived more than 15 years after operation.

Advanced Carcinoma.—While many of the tumors in Group 3 contained mixed cell types, the predominant cell type was used in classification. Of the 66 patients in Group 3, 23 had papilliferous adenocarcinomas. The remaining 43 had the other histologic types, known to have a less favorable prognosis. These will be considered separately.

Papilliferous Adenocarcinoma.—Although ages varied from 3 to 86 years, papilliferous adenocarcinoma in general involved a young age group. Five of the eight males in the group were less than 25 years old and 7 of the 15 females were under 30.

The two cancer deaths (8.7% of this group) occurred in patients in whom spread of the neoplasm was beyond the neck. In each instance the patient died from the local effects of the residual tumor rather than from metastases. One death occurred in the immediate postoperative period and the other within eight months of operation. Of 19 living patients, 9 were 5-year survivors, and two of them were alive more than 10 years after initial therapy. Three of the 19 living patients had had cervical recurrences requiring further treatment.

Papilliferous adenocarcinoma is slowly progressive, tending to invade regional lymphatics earlier than other types of carcinoma. Pulmonary metastases were noted in two cases. In one instance the pulmonary lesions disappeared after thyroidectomy and irradiation of the neck and lungs. This patient had a cervical node recurrence, with local excision and x-ray therapy, and has survived eight years without symptoms and without physical or roentgenographic evidence of recurrence. The other patient with pulmonary metastases died in the immediate postoperative period before adequate irradiation could be given. Metastasis in the skull was present in a third case and was treated by excision and x-ray therapy, and no neoplasm was found clinically six years after the period of initial therapy.

"Lateral Aberrant Thyroid."—Because this condition may be confused with carcinoma of the papilliferous type,[4] it is discussed here.

Enlarged and palpable lymph nodes in the absence of a palpable thyroid gland were found in four instances. These were formerly thought to be lateral aberrant thyroid tissue, but in three of the four cases the nodules proved to be lymph nodes containing metastatic papilliferous adenocarcinoma. In the other case, well-differentiated adenocarcinoma of thyroid origin was found. A primary focus within the thyroid gland, histologically similar to the lymph node metastases, was disclosed by operation in three cases. It was of interest in the fourth case that the surgeon left the grossly normal gland intact and excised only the lateral nodules. Subsequent x-ray therapy and excision of one recurrence in the neck resulted in an eight and one-half year period of survival without evidence of further recurrent or metastatic growth.

The bulk of evidence suggests that the so-called lateral aberrant thyroid is a manifestation of metastatic carcinoma of the thyroid gland in a lymph node. A thorough search will usually reveal the primary tumor, often grossly insignificant, in the homolateral lobe of the thyroid gland. Such lateral masses may be bilateral, and the primary tumor may be in or near the isthmus of the gland.

4. Warren, S., and Feldman, J. D.: Nature of the Lateral "Aberrant" Thyroid Tumors, Surg., Gynec. & Obst. **88**:31-44, 1949.

Nonpapilliferous Carcinoma.—Of the other 43 patients in Group 3 (who had carcinomas of other than papilliferous type), 20 died of cancer of the thyroid, most of them within a year after thyroidectomy. Deaths occurred in direct proportion to the degree of anaplasia. When the types are listed in order of differentiation, adenocarcinoma, with frequent admixtures of other cell types (and showing varying amounts of colloid), made up 20% of the tumors in this group. Medullary adenocarcinoma, with little or no colloid, made up 12%. Poorly differentiated carcinoma was the largest single cell type categorized, with 21%, while poorly differentiated medullary carcinoma and spindle-cell carcinoma were so often associated that these more anaplastic types were considered together and made up 11% of tumors in the group.

Epidermoid carcinomas in the thyroid represent metaplasia from the other types and are always associated with a carcinoma of another cell type if primary in the thyroid. In no instance did the squamous-cell change overshadow the original cell type in our material in the original examination, but adequate follow-up is lacking to reveal whether this feature persists. Extension of squamous-cell carcinoma from

TABLE 6.—*Deaths in Cases of Thyroid Cancer, One Hundred Per Cent Follow-Up*

Group	No. of Patients	Deaths Due To Cancer	Deaths Due To Other Causes
Early carcinoma *	68	0	9
Papilliferous carcinoma †	23	2	2
Nonpapilliferous carcinoma †	43	20	6
Sarcoma	5	5	0

* Grades 1 and 2.
† Grade 3.

the common sites in surrounding tissues (esophagus, larynx, salivary gland, branchial cleft) must always be considered when a squamous-cell carcinoma occurs in the thyroid gland.

In the mixed-cell carcinomas, the course in most cases was that of the most anaplastic cell type present. Hypernephroid cells were present in 10 cases but were predominant in only 1 case. The acidophilic, or Hürthle, cell was present in three cases in Group 3, and was not the prominent cell in any.

Of the 17 living patients, 10 had had at least one recurrence in a cervical lymph node. Only 6 of the 17 patients had survived 5 years, and only 1 of the 6 had survived for 10 years.

All five patients with spindle-cell sarcoma died within one year after operation, four of them within four months after the diagnosis was established.

METASTASES FROM THYROID CARCINOMA

Metastases in cervical lymph nodes were the commonest metastases from carcinoma of the thyroid, and pulmonary metastases were second. The trachea was involved frequently by direct extension. Bony metastases were found in the skull, scapula, ulna, ilium, and vertebral bodies but were not common in our series and were multiple in only one patient. However, in a patient with osseous metastases of unknown origin, carcinoma of the thyroid must be considered.

Autopsies were performed in 24 instances on patients with carcinoma of the thyroid with metastases. In addition to the findings listed in Table 7, metastases were present in skin and voluntary muscle in one patient who had carcinomatosis.

METASTASES TO THE THYROID GLAND FROM OTHER PRIMARY SITES

While the thyroid gland was thought to be an uncommon site for metastatic neoplasms, six cases were found among those in which primary involvement of the thyroid was suspected and thyroidectomy was performed. In three of these cases there was a history of previously diagnosed malignancy without evidence of metas-

TABLE 7.—*Metastases from Thyroid Cancer, Twenty-Four Autopsies* *

	No. of Cases
Lungs	15
Trachea	10
Cervical lymph nodes	5
Paratracheal lymph nodes	5
Adrenal gland (one or both)	5
Neck muscles	4
Liver	4
Mediastinal lymph nodes	4
Esophagus	3
Diaphragm	3
Heart	3
Kidney	2
Vertebral bodies	2

* Pancreas, brain, gall bladder, jejunum, ileum, pleura, periaortic lymph nodes, and mesenteric lymph nodes were each involved in one case.

TABLE 8.—*Origin of Primary Cancers with Metastases in the Thyroid* *

	No. of Cases
Bronchogenic carcinoma	15
Carcinoma of breast	8
Carcinoma of stomach	8
Lymphoblastoma	7
Carcinoma of larynx	5
Carcinoma of cervix	5
Carcinoma of esophagus	4

* Metastasis was present in the thyroid gland in one case each of carcinoma of the gall bladder, rectum, kidney, ureter, prostate, ovary, and branchial cleft. In one case the primary neoplasm was not found.

tasis. In two the patients had had radical mastectomy for carcinoma of the breast three to four years previously. Another patient had bronchogenic carcinoma. The other three had no known primary neoplasm. One proved to have a lymphoblastoma, one had a squamous-cell carcinoma of the submaxillary gland with extension into the thyroid, and the third showed a mucin-forming adenocarcinoma of unknown origin. In at least one case the operation hastened death, and in none was life prolonged.

Of 6,500 autopsies performed during this 15-year study period, 60 disclosed metastases to the thyroid gland. The primary sites of the neoplasms are summarized in Table 8. In only one instance was the only metastatic lesion found in the thyroid gland, the stomach being the primary site in this case. All the metastases to the thyroid gland in this series occurred in nodular goiters.

In secondary neoplasia of the thyroid gland, regional extension or metastasis may account for involvement from carcinoma of the larynx, esophagus, pyriform sinus, branchial cleft, or salivary gland. The common occurrence of lymphocytes in the thyroid in the Great Lakes area makes lymphoblastomatous change in the thyroid a logical finding. However, metastases from the lung, breast, gastrointestinal tract, and other sites were not unusual.

CLINICOPATHOLOGIC CORRELATION

Early Signs.—The early phase of cancer of the thyroid can be diagnosed only on a histologic basis, being clinically indistinguishable from the nodular goiter in which it most commonly develops. Accessibility should render the diagnosis of nodular thyroid readily possible, but in only 61 cases of the total 139 was cancer definitely suspected clinically. Removal of the carcinomatous nodules at this stage will prevent later infiltrative growth and metastasis.

Advanced Signs.—After invasion of the outer capsule of the thyroid gland, physical signs develop more rapidly. Fixation to contiguous structures occurs, and the neoplasm extends along the vessels and lymphatics. Neighboring lymph nodes may become fused and on physical examination mistakenly be thought to be part of the nodular gland. As veins become invaded, pulmonary dissemination may be revealed by x-ray examination. The recurrent laryngeal nerves or the trachea may be compressed or infiltrated, hoarseness and dyspnea resulting. However, hoarseness and dyspnea, as well as dysphagia and/or choking sensations, are late symptoms. The skin overlying the thyroid area may become infiltrated, reddened, and ulcerated by the larger, far-advanced lesions.

PROGNOSIS

Statistically, malignant disease of the thyroid may not be as spectacular a problem as malignant disease of the stomach, lung, or brain, but it nevertheless was the cause of death in 33.85% of the patients in Group 3 (46.5% if patients with the slower-growing papilliferous adenocarcinoma are excluded) and 100% of the group with sarcoma. It is an unpleasant cause of death by slow strangulation and suffocation. Although some patients have survived 10 years or more without recurrence, and others with recurrence have lived for several years, most of the deaths occurred within a year and many within weeks or months of the time of diagnosis.

Only 1 of the 27 deaths which resulted from thyroid cancer occurred in a patient under 39 years of age. This patient was the 3-year-old boy who died of extensive local neoplasm before adequate therapy could be instituted. Inasmuch as 40% of the patients were less than 40 years of age, statistically speaking carcinoma of the thyroid in the younger age group would appear to have a more favorable prognosis.

Likewise, survival studies show that 18 of the 27 deaths occurred within nine months of the date of operation and diagnosis and the others within three and one-half years. This fact suggests that in these cases the growth was extensive when first seen and that an attempt should be made to remove the neoplasm in an earlier stage, when cure may be possible. One patient survived 8½ years from the time of diagnosis.

Status of Cervical Lymph Nodes as a Prognostic Sign.—Since the cervical lymph nodes are the commonest site of metastasis from carcinoma of the thyroid, a survey of the patients with lymph node metastases was made (Table 9).

In the group of 23 patients with papilliferous adenocarcinomas, there were 12 patients with lymph nodes which contained metastases at the time of the original operation. Of these 12 patients, 3 had cervical node recurrences later, whereas no recurrences were noted in the 11 patients who had no "positive" nodes originally. There was one death each in the "positive" and the "negative" node groups. Of the 12 patients with initial cervical node metastasis, 10 were under 30 years of age.

In the group with nonpapilliferous advanced carcinoma there were 12 patients with cervical nodes which contained metastatic carcinoma. Of these 12 patients, 5 have died of cancer. Among the patients yet living who had metastases in lymph nodes at the original operation, four have had cervical lymph node recurrences. There were 15 cancer deaths and six cervical lymph node recurrences among those who had no "positive" nodes at the time of operation.

TABLE 9.—*Status of Cervical Lymph Nodes as Prognostic Sign*

	Cases	Recurrences	Deaths
Papilliferous adenocarcinoma	23		
"Positive" nodes	12	3	1
"Negative" nodes	11	0	1
Nonpapilliferous carcinoma	43		
"Positive" nodes	12	4	5
"Negative" nodes	31	6	15

Statistically, recurrence was more frequently noted in those who had metastases in the cervical nodes at the original operation, but the death rate was no higher for this group than for the group with "negative" nodes.

Favorable Factors in Prognosis.—The early-carcinoma group, whose neoplasms were removed before widespread invasion and/or metastasis occurred, had the best prognosis. Cancer of the thyroid in the younger age group, in general, had a more favorable outlook. This may be attributed to earlier diagnosis in their cases, but was due in part to the higher incidence of the papilliferous type of adenocarcinoma. Radioactive iodine concentration in the well-differentiated neoplasm which produced colloid was usually appreciable. This concentration may be associated with better prognosis. Survival for a period longer than 3½ years carried the patient through the time when most deaths occurred from carcinoma of the thyroid, although recurrence may be found for as long as 14 to 16 years.[5]

Adverse Factors in Prognosis.—If the diagnosis of carcinoma of the thyroid was apparent from the history and physical examination alone, the prognosis was usually poor. Rapid growth, hoarseness, dysphagia, and dyspnea were late manifestations in cases of cancer of the thyroid. All but one of the deaths in this series

5. Watson, W. L., and Pool, J. L.: Cancer of the Thyroid, Surg., Gynec. & Obst. **70**:1037-1050, 1940.

occurred in the middle and older age groups; therefore, the diagnosis of cancer of the thyroid in these age groups heralded a poorer prognosis. Deaths were directly related to the degree of anaplasia of the neoplasm. Metastases beyond the cervical lymph nodes usually were thought to indicate a hopeless prognosis, but in two cases of osseous metastases and in one of pulmonary metastases, "cures" had been effected by radiation therapy and the patients showed no evidence of neoplasm six to eight years after therapy. (The neoplasms were of papilliferous type in each of these cases.)

THERAPY

Prophylaxis.—Inasmuch as nodular thyroid and carcinoma are definitely related, a general program for treatment of patients with nodular goiters has been followed. A nodule in the thyroid gland suggests abnormal growth, and operative removal may be justified and indicated in a majority of instances. This observation does not imply that immediate operation is imperative, or that a period of observation is unwarranted. On the contrary, many of the cases of nodular goiter were followed for a number of months or years, particularly when coexistent disease, age, and other factors contraindicated operation. However, operation was not delayed if malignancy was suspected.

In a thyroid gland containing a single nodule the involved lobe is removed totally, the laryngeal nerve and parathyroid glands being preserved. Immediate examination of the solitary nodule by the pathologist is indicated, and if the findings are positive, a total thyroidectomy should be done. If this examination is negative, the contralateral lobe is preserved and the patient followed clinically at regular intervals.

In multinodular glands, bilateral involvement is the rule, and a near-total resection is often required. Total resection of the gland has not been considered mandatory. A small amount of "capsular" tissue left adjacent to the trachea may spare important anatomical structures and obviate requirement for desiccated thyroid postoperatively. If no normal thyroid tissue is noted and a total resection is performed, oral replacement therapy is later instituted.

In cases in which microscopic examination reveals localized carcinoma (Groups 1 and 2), no additional therapy is given, but the patient is followed at intervals for evidence of recurrent neoplasm.

Definitive Therapy (Primary Surgery).—Primary malignant disease of the thyroid gland is frequently suggested for the first time at the operating table. Histopathologic study by frozen-section technique may clarify the situation, but a diagnosis by this means may not be accurate in all instances, even when made by an expert pathologist, and mature clinical judgment is therefore required. In cases of Riedel's struma and Hashimoto's disease an especially difficult differential diagnostic problem may be presented. If a diagnosis of carcinoma is mistakenly made and total thyroidectomy performed on that premise, the laryngeal nerves and/or the parathyroid glands may be sacrificed. In cases of doubt, a subtotal thyroidectomy is indicated. If subsequent histopathologic sections reveal carcinoma, prompt reoperation will effect total thyroidectomy.

In known cases of carcinoma of the thyroid, a total thyroidectomy is done, other structures being sacrificed as required in the attempt to remove the cancer com-

pletely. All detectable adjacent and enlarged cervical lymph nodes are excised. Radical neck-gland dissection is not done routinely, as we have found no advantage to this procedure in cases of thyroid malignancy. Occasionally, when widespread unilateral neoplastic involvement of the cervical lymph nodes is present, lymph node dissection is performed.

Total removal of the thyroid gland which contains carcinoma may be indicated for the following reasons: 1. The procedure offers an opportunity for complete removal of the neoplasm. 2. Complete pathologic examination of the tissue is possible. 3. If the histologic pattern and radioactive iodine uptake studies are favorable, therapeutic I^{131} will concentrate in metastases rather than in any normal thyroid tissue remaining in the neck.

Irradiation Therapy.—X-ray therapy is thought to be a necessary adjunct in all cases except those in which complete excision appears probable. Groups 1 and 2 therefore received no x-ray therapy except when recurrent neoplasm appeared.

At least 3,000 r to each of two lateral cervical ports has been most effective. The therapy is administered at the discretion of the radiologist.

The more undifferentiated neoplasms of the thyroid gland seemed to respond least well to x-ray therapy, and occasionally the tumors appeared to progress more rapidly, i. e., the fusocellular carcinomas and sarcomas. The most favorable response to irradiation occurred in patients with papilliferous adenocarcinomas, in whom even distant metastases in lung or bone occasionally regressed and disappeared with apparent "cure" after x-ray or I^{131} therapy.

Surgery for Recurrences.—In cases of advanced or locally extensive carcinoma, complete removal is often impossible. Surgical decompression and tracheotomy become necessary for palliation in these cases. The effect, although immediately gratifying, is usually short-lived, and the patients die within a few weeks or months.

In less-advanced cases, local recurrence in the cervical lymph nodes is not uncommon. These neoplasms are excised as they appear; irradiation is utilized in most instances after surgical treatment. Some of the patients have had three locally recurrent neoplasms excised, with protracted longevity the rule. One of this group of patients died of carcinoma.

Radical Neck Dissections.—There were only five cases of radical neck gland dissection in the series, and one of the dissections was done elsewhere for a cervical metastasis. This small series may not have statistical significance, but the results with combined surgical and x-ray therapy and the clinical follow-up of the patients with and without cervical node metastases led to the conclusion that the routine use of radical neck gland dissection may not be warranted. As indicated, if unilateral cervical lymph node involvement is extensive, a radical neck gland dissection may be included with the primary operation. Only three such operations were done as part of the primary surgical procedure in this series.

SUMMARY

A review of the malignant neoplasms in 1,928 consecutive cases of thyroidectomy performed between 1935 and 1950 at the University of Michigan Hospital has been summarized and a comparison made between early and advanced carcinomas.

The diagnosis of early carcinoma of the thyroid differs with the experience and philosophy of the pathologist. However, early carcinoma of the thyroid may be accurately diagnosed by careful histopathologic study, and the criteria for the diagnosis of early carcinoma are presented.

The thyroid nodule should be evaluated by the pathologist and not according to its future course in the neck of the patients, since it is only by removal of early carcinoma that prevention of infiltrative growth and metastasis can be accomplished. The thyroid glands in Groups 1 and 2 contained early carcinoma in the only favorable state for cure. It is impossible to predict which of the locally malignant tumors will metastasize or how quickly such a change may occur.

Deaths from cancer of the thyroid are directly proportional to the ease of clinical diagnosis and to the degree of anaplasia noted histologically.

Cervical lymph node metastases have no constant prognostic value in patients with carcinoma of the thyroid.

Mortality for younger patients is low, perhaps owing to earlier diagnosis and to the prevalence of well-differentiated types of carcinoma in this group.

Routine radical neck gland dissections may not be indicated.

CRITERIA FOR THERAPY OF MALIGNANT THYROID LESIONS WITH I^{131}

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IT HAS been approximately seven years since radioactive iodine was first used in therapeutic amounts in the treatment of thyroid carcinoma. Although this period is too short for any final evaluation, it has been long enough to enable the physician to formulate definite criteria for its administration. The original enthusiasm for treating all thyroid cancers with I^{131} has now been rightfully replaced by an investigative approach to each individual case. Since the limitations of I^{131} therapy are many, no patient should be denied other therapy of proved value in the hope that therapeutic doses of radioactive iodine will bring about lesion resolution.

We report our experiences with 47 consecutive cases of thyroid carcinoma in a representative university center over a four-year period. For clinical purposes the lesions are microscopically classified into papillary, adenomatous, and undifferentiated carcinomas. There were 13 cases of papillary carcinoma, usually with a few adenomatous elements interspaced, and 17 were cases of adenocarcinomas with varying amounts of colloid formation. The remaining 17 cases were of the undifferentiated type.

None of the undifferentiated or papillary types of carcinoma showed any appreciable uptake of I^{131} in the primary or metastatic lesions. Of the 17 adenocarcinomas, 8 presented metastases, and 3 of these showed sufficient uptake for I^{131} therapy to cause diminution in size of the lesions. These 3 represent 7% of the total of 47 cases and are briefly reported herewith.

CASE 1.—W. V., a white boy, was seen at the age of 12 with an adenocarcinoma of the thyroid with cervical lymph node involvement, diffuse pulmonary metastases, and tracheal compression, the last requiring a tracheotomy. Pulmonary biopsy with radioautographs revealed uptake of I^{131} (Fig. 1), and 800 mc. were given over a four-year period. Body scanning reflected the diffuseness of the pulmonary lesions (Fig. 2). Intermittent thyroid medication became necessary to relieve a state of catatonic schizophrenia produced by prolonged myxedema. Comparison of his original x-rays with the most recent (Fig. 3) shows definite diminution of the lesions. Three additional lung biopsies have been performed. The tracheotomy tube has been removed after being in place for three years. His growth and mental development have been entirely normal.

CASE 2.—W. H., a 62-year-old white woman, underwent a subtotal thyroidectomy in 1947 at another hospital for a nontoxic nodular goiter. A fetal adenoma was removed. Two years later a pulsating manubrial mass was noted, and the patient was referred for I^{131} studies. Uptake

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From the Department of Surgical Research, The Medical Center, Ohio State University College of Medicine.

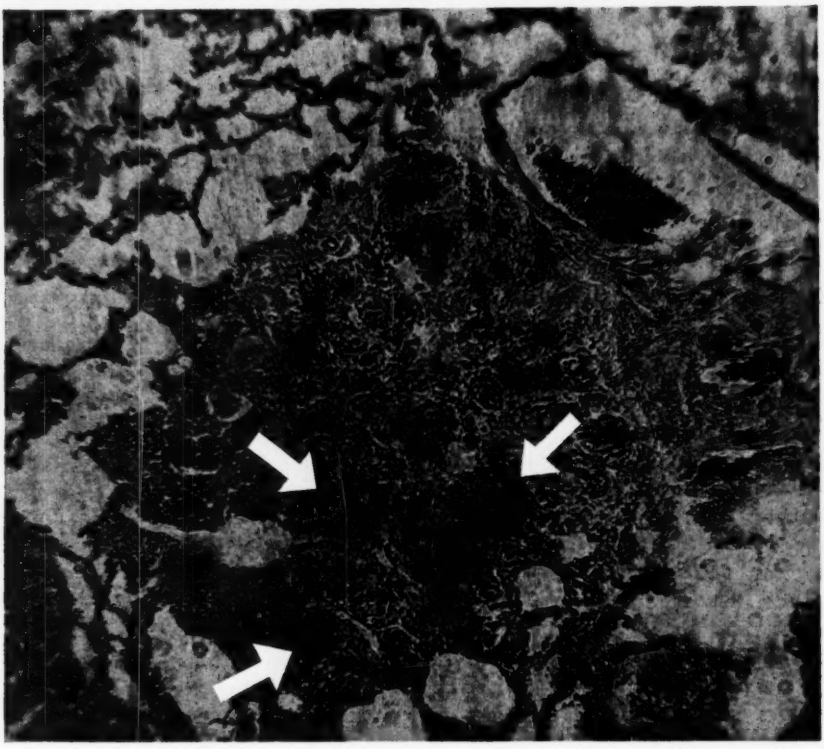

Fig. 1 (Case 1).—Radioautograph of functioning pulmonary metastasis. Pulmonary biopsy was performed 10 hours after 25 mc. of I^{131} was administered; only certain areas of the tumor take up I^{131}.

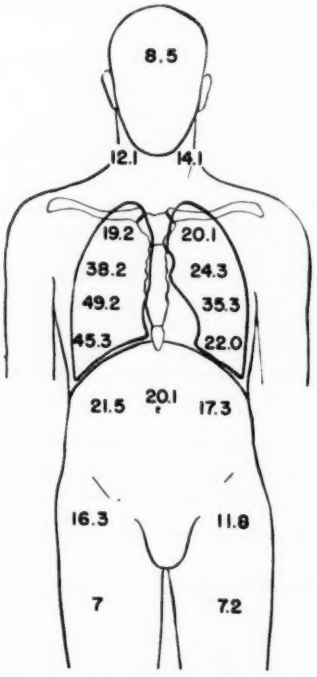

Fig. 2 (Case 1).—Body scanning in counts per second 17 days after 100 mc. of I^{131} was administered.

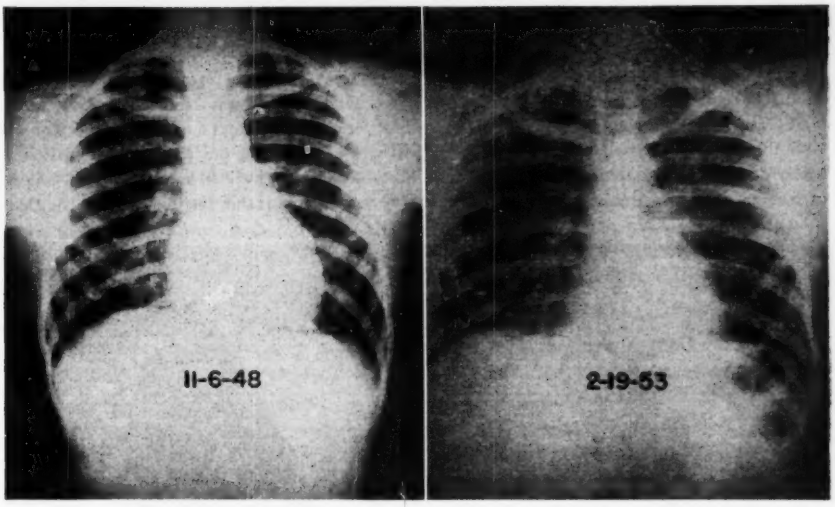

Fig. 3 (Case 1).—Roentgenograms taken before and after the administration of 800 mc. of I^{131} in a four-year interval.

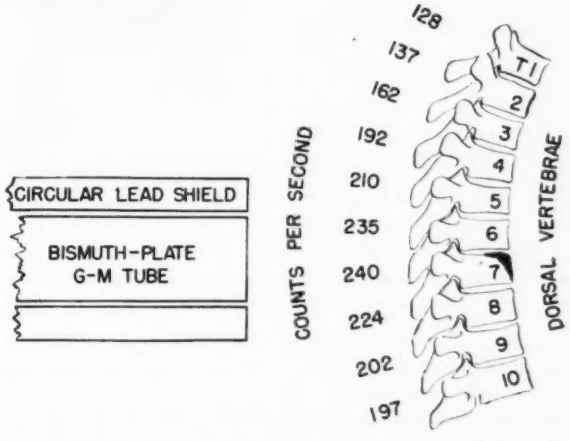

Fig. 4 (Case 2).—Scanning of thoracic vertebra six days after administration of 75 mc. of I^{131}. This lesion was later confirmed by x-rays.

was demonstrated in both the neck area and the metastasis. A biopsy and radioautograph ascertained the uptake, and 300 mc. of I^{131} were administered during the next 12 months. The manubrial mass was reduced to 25% of its original size and was then surgically removed. During therapy a metastatic deposit was found by body scanning in the seventh thoracic vertebra (Fig. 4). X-rays confirmed the lesion, which is now decreasing in size under therapy. A total of 700 mc. of I^{131} has been administered.

CASE 3.—V. K., a 64-year-old white woman, underwent a subtotal thyroidectomy in 1937 at another hospital for a nontoxic nodular goiter. A recurrent nodule was removed in 1945, without evidence of malignant growth. In 1947 a nodule recurred, and carcinoma was suspected. In 1949 the patient sustained a fracture to her clavicle while combing her hair. On admission a tracer dose was administered, but the clavicular lesion took up no I^{131}. A biopsy revealed adenocarcinoma from the thyroid. Other metastases were suspected, and for this reason surgical

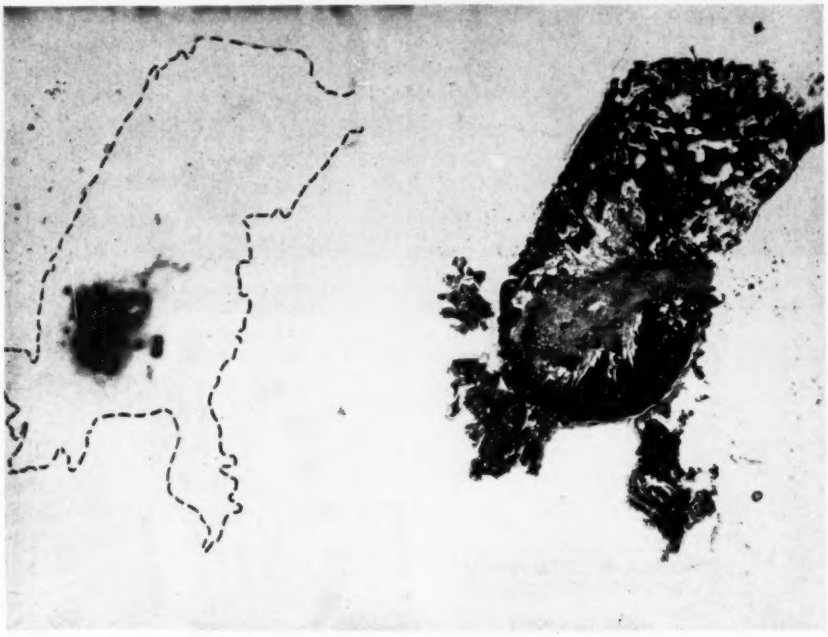

Fig. 5 (Case 3).—Radioautograph of surgical specimen obtained by three-day exposure to lantern slide plate. Only the encircled tumor tissue took up I^{131}.

removal of the lesion was postponed for one year, during which time 510 mc. of I^{131} were given, and the clavicular lesion began to take up I^{131}. The lesion was then surgically removed and radioautographs confirmed its function (Fig. 5). At present the patient presents a recurrence of her lesion in the neck which takes up nontherapeutic amounts of I^{131}.

COMMENT

As a result of clinical investigation, we feel, in common with other authors, that there are three concrete indications for extensive therapy with I^{131}.

First Indication.—By far the most distinct indication for I^{131} therapy lies in the functioning inoperable metastases. Microscopically these tumors are usually adenocarcinomas, or papillary adenocarcinomas with a fair amount of colloid

present. The amount of uptake is not necessarily directly proportional to the amount of colloid. Indeed, the patient in Case 2 took up a significant amount of I^{131} in a single metastasis, and the microscopic section revealed a microfollicular arrangement with minimal colloid. Each one of our three patients who underwent intensive I^{131} therapy had an adenocarcinoma with some degree of colloid formation.

It is obvious that these lesions should be inoperable. There is seldom an indication to treat a thyroid carcinoma with I^{131} when it can be safely and adequately removed by surgery, thereby making unnecessary prolonged periods of myxedema and exposure to radiation. Occasionally I^{131} is given for the primary tumor or local recurrence thereof. If a fairly well-differentiated adenocarcinoma has extended into the surrounding neck tissue to such an extent that surgical removal is impossible, I^{131} should be tried before other means of irradiation are employed. In our experience, patients with differentiated adenocarcinomas present themselves for surgery before the neck lesion has become inoperable.

Second Indication.—Radioiodine is used in cases of nonfunctioning inoperable metastatic lesions to destroy the normally functioning thyroid tissue which may remain, whereupon the thyroid-stimulating hormone of the anterior pituitary may encourage the metastatic deposits to take up and retain a significant amount of I^{131}.

Injections of thyroid-stimulating hormone have increased the uptake of I^{131} in some cases. Rall and his associates [1] report the use of the hormone in 16 cases, in 5 of which there was increased uptake. Thiouracil also causes a stimulation of neoplastic thyroid cells and thereby increases the uptake of I^{131}, although in an indirect manner. The patient in Case 2 was given methimazole (Tapazole), without any noticeable increase in uptake.

Third Indication.—Heavy tracer or therapeutic doses of I^{131} are, on occasion, given to make possible a study of the distribution of uptake in surgical or autopsy specimens. Patients with a known diagnosis of carcinoma of the thyroid have been given tracer doses preoperatively to prepare radioautographs of the surgical specimen. The distribution of I^{131} at necropsy in body tissue has been studied by Godwin and his associates.[2] No significant uptake of I^{131} was found by radioautographs in any body organs other than thyroid or thyroid metastases after therapeutic doses.

From the clinical research in thyroid carcinoma, several additional observations are pertinent. Radioiodine is of little help in diagnosing thyroid carcinoma in a patient with a nodular goiter without metastases. The administered drug will localize to a certain extent in the normal thyroid gland which surrounds or is encased by the tissue suspected of being malignant. Usually the percentage of uptake of I^{131} in the region of the thyroid will be below 30% and frequently below 10%. Scanning the neck area with a lead-shielded Geiger tube or scintillation counter may well show a nodular area with decreased uptake. Whether this is a colloid nodule with degeneration or a malignant nodule cannot be definitely ascertained until surgery is performed, and in some cases not until the microscopic sections are studied.

1. Rall, J. E.; Miller, W. N.; Foster, C. G.; Peacock, W. C., and Rawson, R. W.: The Use of Thiouracil in the Treatment of Metastatic Carcinoma of the Thyroid with Radioiodine, J. Clin. Endocrinol. **11**:1273-1280 (Nov.) 1951.

2. Godwin, J. T.; Duffy, B. J., Jr.; Fitzgerald, J. J.; Trunnell, J. B., and Rawson, R. W.: Pathological Effects and Radioautographic Localization of I^{131} in Humans: Postmortem Study in 9 Patients, Cancer **4**:936-951 (Sept.) 1951.

Another misconception that has been brought to light and must constantly be kept in mind is that in patients presenting metastases from an unknown source, the failure of I^{131} to localize in these lesions does not rule out the possibility of their being of thyroid origin. Indeed, in our series, only one of eight patients with known metastases of an adenocarcinoma showed uptake of a heavy tracer dose in a metastatic lesion before the remaining normal thyroid tissue was destroyed or removed.

If therapy with I^{131} is indicated, we believe the following dosage schedule is preferable. An initial dose of 25 to 50 mc. is given. This will occasionally produce signs of tracheitis and subacute thyroiditis in about three to six weeks. This is not a serious complication and is easily tolerated by the patient. Six to eight weeks later a dose of 100 mc. is given and is repeated every four to six months until the desired effect is obtained or until the lesions no longer take up I^{131}. The patient will be myxedematous in several months with this schedule and should be kept in that state if he can tolerate it.

There are times when long-standing myxedema will cause intolerable conditions, such as a state of catatonic schizophrenia as in Case 1. In these instances we allow the administration of desiccated thyroid, 2 to 3 grains (0.12 to 0.20 gm.) daily, discontinuing this medication six weeks prior to another therapeutic dose.

Trunnell and his associates [3] report a fatality from a panhematopenea following the administration of 638 mc. of I^{131} over a six-month period. We have administered 700 mc. over a three-year period in two cases and 800 mc. over a four-year period in another without any demonstrable damage to bone marrow, kidney, liver, or other organ systems.

In well-selected cases, I^{131} has proved definitely valuable in offering palliation and in some cases unquestionable diminution in size of the lesions with microscopic destruction of malignant tissue. As previously stated, all three of our patients presented adenocarcinomas with varying amounts of colloid formation. Two had undergone previous subtotal thyroidectomy for a nontoxic nodular goiter and showed no definite carcinoma on the microscopic examination of the surgical specimen at that time. It was not until several years later, when metastatic lesions presented themselves, that they were recognized as malignant lesions. It was then that microscopic reexamination of the previously removed tissue revealed in one case a nodular colloid mass with muscle invasion, and in another, a fetal adenoma. These two cases, among others, serve to show the difficulty in making a correct diagnosis in every instance and the inability of the pathologist to make positive predictions. How many such cases as the foregoing will appear in the next 10 years?

Present-day study of I^{131} therapy in thyroid carcinoma is concerned mostly with finding a means to increase the meager uptake in lesions, usually the moderately differentiated adenocarcinomas. The work with thyroid-stimulating hormone and thiouracil derivatives has been stimulating, but the amount of irradiation that can be delivered to the malignant lesion is far short of cancercidal doses in the vast majority of instances. Therefore, until these shortcomings are overcome, other ways

3. Trunnell, J. B.; Marinelli, L. D.; Duffy, B. J., Jr.; Hill, R.; Peacock, W., and Rawson, R. W.: The Treatment of Metastatic Thyroid Cancer with Radioactive Iodine: Credits and Debits, J. Clin. Endocrinol. **9**:1138-1152 (Nov.) 1949.

must be sought to decrease the mortality and morbidity of this type of carcinoma. It would seem that for the present and in the forseeable future it will be up to the surgeon to improve statistics. This can come only through the earlier removal of nodular goiters and adequate surgery for known carcinomas.

SUMMARY AND CONCLUSIONS

Forty-seven consecutive cases of thyroid carcinoma have been studied to determine the criteria for I^{131} therapy. In only three cases was the necessary indication present, that of functioning metastases. In all of these cases the patients received benefit from I^{131} therapy. All lesions were adenocarcinomas with colloid formation. No papillary or undifferentiated lesions ever retained enough I^{131} to warrant continued therapy. When in only 3 out of 47 cases, or 7%, the patients are amenable to I^{131} therapy, even though dramatic, it is obvious that early and adequate surgery is still the best weapon in the fight against this form of carcinoma.

CAROTID BODY TUMORS

Report of Twelve Cases, Including One Case with Proved Visceral Dissemination

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THERE is no more controversial tumor occurring in the neck than that arising from the carotid body. The surgeon faced with the treatment of this entity faces conflicting opinions and whether such lesions are benign or malignant and whether or not any attempt should be made at removal. The crux of the matter lies in the close relationship of the tumor to the carotid artery. The serious sequelae that ensue from ligation of this structure, such as death and crippling permanent neurologic disturbances, have distressed all serious-minded surgeons.

The thesis of our paper is, first, that carotid body tumors are not totally benign, as has been claimed, but if followed long enough are found to cause serious trouble either by local invasion of surrounding structures or by distant dissemination of disease; second, that with a better understanding of the precise relationship of the tumor to arterial wall components, it is possible to remove the lesion without disrupting arterial continuity if the patient is operated upon reasonably early, and, finally, that in the event of damage to the artery during attempted removal, techniques are now available and should be used that will permit restoration of continuity of the carotid with resultant maintenance of blood supply to the brain.

SYMPTOMATOLOGY AND INCIDENCE

The chief complaint of patients with this entity is usually simply a "lump in the neck." Although characteristically discovered in early adult or middle age, the tumor can occur at almost any age. Our 12-year-old patient, a white girl, was younger than any we have encountered in the literature. There is little difference in distribution between the sexes in larger series, yet in our own group of 12 cases only 2 occurred in males. The mean duration of symptoms was 4.5 years, and the average age when the patients sought medical care was 50 years.

The patients' histories support the concept that the habit of this entity is continued albeit slow growth. In the early stages (until the tumor begins to exceed 5 to 6 cm. in diameter) few or no complaints other than the neck mass are noted.

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From the Department of Surgery and the Bonfils Tumor Clinic, University of Colorado School of Medicine.

However, with increase in size, pain of a rather mild or moderate intensity appears. With further extension of the tumor, homolateral laryngeal paralysis from vagus nerve invasion, homolateral paralysis of the tongue from hypoglossal nerve invasion, and Horner's syndrome from sympathetic nerve invasion may appear. At still later stages, spread to the regional lymph nodes of the neck and even distant dissemination may occur.

Although some authors have stated that upward of 300 carotid body tumors have been reported, our survey of the literature covering the years from Reigner's first case, reported by Marchand in 1891,[1] to March, 1952, leads to the belief that there has been duplication of case reports and that the true figure is in the neighborhood of 275. To these cases we add 12 of our own from the Bonfils Tumor Clinic of the University of Colorado and from private practice in the period 1938-1952. Hence, it is seen that if the importance of carotid body tumors rested solely on their incidence, little justification would exist for spending much time on the problem, since it is certain that other causes for neck masses are overwhelmingly more frequent than such tumors.

DIAGNOSIS

Because the commenest complaint is "lump in the neck," the diagnostic appraisal must encompass all the possibilities that might explain the presence of such a mass. The list is a long one and includes such phenomena as metastasis to the cervical lymph nodes from an unrecognized primary tumor within the oral cavity or homolateral thyroid, branchiogenic cysts, aneurysms, salivary gland tumors, and primary tumors of soft part origin, such as neurofibroma, lipoma, and fibrosarcoma. On the basis of chance alone the commonest explanation for an asymmetrical cervical enlargement in an adult is a metastasis from an intraoral primary cancer.[2] Therefore, the most logical way to start examination is a thorough exploration of the mouth and pharyngeal cavities, employing direct vision, palpation, and mirror examination of the hidden recesses of the pharyngeal cavity and base of the tongue. The history of the long-term presence of the mass in the neck, averaging seven years in a large series of cases,[3] is of considerable help, since it is not the nature of metastatic cancer in the neck to remain in a semistationary condition over such a long period.

If these steps are nonproductive, attention should then be directed to the mass itself. Much has been written about the supposed unique method of fixation of carotid body tumors which permits them to be moved in a lateral plane but not in a perpendicular plane. Indeed, in some cases this does appear to be a helpful diagnostic feature. However, in our experience such a sign is seldom marked enough to be considered pathognomonic. Similarly, variations in physical characteristics such as induration, presence or absence of pain and tenderness, "discreteness," or a

1. Marchand, F.: Beiträge zur Kenntniss der normalen und pathologischen Anatomie der Glandula carotica und der Nebennieren, Internat. Beitr. wissensch. Med. Festschrift. R. Virchow **1**:535, 1891.

2. Martin, H., and Morfit, H. M.: Cervical Lymph Node Metastasis as the First Symptom of Cancer, Surg., Gynec. & Obst. **78**:133, 1944.

3. Pemberton, J. DeJ., and Livermore, G. R., Jr.: Surgical Treatment of Carotid Body Tumors: Value of Anticoagulants in Carotid Ligation, Ann. Surg. **133**:837, 1951.

"rubbery feeling" when used as a basis for specific diagnosis are attended with such a high degree of inaccuracy as to hardly justify burdening the mind with these questionable diagnostic criteria.

As in the case of other tumors, then, the physician finds himself in need of histologic proof (biopsy). Although aspiration biopsy has had both strong proponents and strong opponents, we have found the method extremely valuable in evaluating the nature of neck masses, and in our clinic its use has resulted in a correct diagnosis in 90% of the instances in which it has been employed.[4] While it is true that aspiration biopsy in cases of carotid body tumors has only rarely resulted in a definitive diagnosis, nevertheless its value is real even when the diagnosis is not definitive. As one progresses through the steps outlined and fails to find a tumor within the oral cavity and fails also to obtain satisfactory tissue for diagnosis by an aspiration biopsy, the case for the commoner explanations of the neck mass becomes increasingly weaker and the probability of the more unusual explanations, such as a carotid body tumor, becomes stronger.

Reaching an impasse with all diagnostic measures herein described, the surgeon then should recommend surgical exploration. In the majority of our cases an accurate diagnosis was not established until operation, and this seems to have been the experience of others. When the diagnosis of carotid body tumor was suggested on the patient's first visit to our clinic, it was usually by one of the more inexperienced members of the group, such as a medical student or intern. Such persons will think of carotid body tumors as one of the first diagnostic possibilities, forgetting about the commoner conditions. Experienced workers in this field recognize the high odds against such a clinical diagnosis, and this fact has led to a paradox which can be expressed by saying that the degree of accuracy in the recognition of carotid body tumors prior to operative removal seems to vary inversely with the experience of the examining physician.

PHYSIOLOGICAL EFFECTS OF INTERRUPTING THE CAROTID ARTERY

Great diversity of opinion exists in the literature concerning the risk of ligation of the common carotid artery, the internal carotid artery, and the combination of common and external carotid arteries. It is generally agreed that ligation of the external carotid alone causes no significant sequelae. Ligation of the common carotid alone is primarily done in the treatment of neoplasms and of intracranial aneurysms. By and large, it appears that the risk of ligation for neoplasm is considerably greater than the risk for aneurysm. Thus, for neoplasm, Vosseler and Ficarra[5] had a mortality rate of 19%, Pemberton and Livermore[3] 30%, Lahey

4. Prior to the acceptance of cytological studies on smears, excreta, effusions, and so on, we encountered considerable reluctance on the part of pathologists to make a diagnosis on the basis of the scanty material sometimes obtained from a needle biopsy. As the years have rolled by, however, and the pathologist has been forced by the clinician to express an opinion on the nature of one or two scattered cells taken by the smear technique, the pathologist has grown more tolerant, and now he seems to feel that the surgeon submitting material obtained in a needle biopsy is not such a bad person after all.

5. Vosseler, A. J., and Ficarra, B. J.: Ligation of Carotid Arteries for Advanced Malignant Neoplasms of the Head and Neck, Arch. Surg. **58**:35, 1949.

and Warren [6] 37.5%, Martin and associates [7] 40 to 50%, Watson and Silverstone [8] 55%, and MacComb [9] 58%. On the other hand, for intracranial aneurysm, Bassett and Gass [10] report 4.5%, Rogers [11] 4.5%, Dandy [12] (internal carotid) 4%, and Sweet, Sarnoff, and Bakay [13] 5.1%. As we are here considering the risk of carotid ligation in the treatment of carotid body tumor, the higher risk rates associated with ligation for neoplasm must be considered as probably valid.

It has been felt by many authors (Dorrance,[14] Keegan,[15] and Rogers [11]) that ligation of the common carotid with the external carotid intact is less dangerous than ligation of the internal carotid, because of the possibility of retrograde flow via the external carotid. Conley [16] has even suggested anastomosis between internal and external arteries after bulb excision on the basis of this theory. The statistical evidence available, however, is far from convincing. Moreover, in the beautifully executed pressure studies on 22 patients with intracranial aneurysm by Sweet, Sarnoff, and Bakay,[13] opening of the external carotid after ligation of the ipsilateral common carotid rarely caused an increase in pressure in the internal carotid; in some instances it even caused a fall (Fig. 1). On the basis of present evidence, then, it does not appear to be justifiable to state that common carotid ligation carries a risk significantly different from that of internal carotid ligation. In any event, as regards carotid body tumor, because of its location in the notch of the vessel, carotid ligation almost always means triple ligation, and, therefore, maximal risk must be assumed.

The ill effects from carotid body ligation may become manifest at once or may develop hours or even days later. A number of causes of delayed symptomatology have been suggested. In our opinion, the evidence is strong in favor the concept that ligation causes immediate diminution in blood flow to the brain. Sweet and associates [13] clearly showed that there is an average fall of 57% in integrated mean pressure distally following internal carotid ligation. If the pressure falls to 30%, neurologic sequelae can be confidently expected. With the reduced blood flow, cerebral anoxia occurs, with resultant cellular damage and softening. The speed

6. Lahey, F. H., and Warren, K. W.: Long Term Appraisal of Carotid Body Tumors with Remarks on Their Removal, Surg., Gynec. & Obst. **92**:481, 1951.

7. Martin, H.; Del Valle, B.; Erhlich, H., and Cahan, W. G.: Neck Dissection, Cancer **4**:441, 1951.

8. Watson, W. L., and Silverstone, S. M.: Ligature of Common Carotid Arteries in Cancer of the Head and Neck, Ann. Surg. **109**:1, 1939.

9. MacComb, W. S.: Carotid Body Tumors, Ann. Surg. **127**:269, 1948.

10. Bassett, R. C., and Gass, H. H.: Ligation of Internal Carotid Artery for Aneurysmal Lesions of Circle of Willis, J. A. M. A. **147**:842, 1951.

11. Rogers, L.: Ligature of Arteries, with Particular Reference to Carotid Occlusion and the Circle of Willis, Brit. J. Surg. **35**:43, 1947.

12. Dandy, W. E.: Results Following Ligation of the Internal Carotid Artery, Arch. Surg. **45**:521, 1942.

13. Sweet, W. E.; Sarnoff, S. J., and Bakay, L.: A Clinical Method for Recording Internal Carotid Pressure: Significance of Changes During Carotid Occlusion, Surg., Gynec. & Obst. **90**:327, 1950.

14. Dorrance, G. M.: Ligation of the Great Vessels of the Neck, Ann. Surg. **99**:721, 1934.

15. Keegan, J. J.: Carotid Ligation for Intracranial Arteriovenous Aneurysm, Surg., Gynec. & Obst. **57**:368, 1933.

16. Conley, J. J., and Pack, G. T.: Surgical Procedure for Lessening the Hazard of Carotid Bulb Excision, Surgery **31**:845, 1952.

of the development of this lesion is a function of the degree of circulatory insufficiency. Although in some cases postoperative thrombosis in the distal arterial segment may occur, as suggested by Dandy,[12] this finding has been only occasionally confirmed in autopsy reports of other investigators. The use of postoperative anticoagulants, therefore, as advocated by Pemberton and Livermore,[3] while possibly increasing the factor of safety, should not be considered as eliminating the dangers inherent in ligation.

Neither can carotid ligation be made safe by preliminary intermittent digital compression of the artery (Matas maneuver) or by stellate ganglion block, nor will gradual preligation occlusion of the vessel be effective. One of us (H. M. M.) recalls a case in which, as a preliminary operative step, a Crile clamp was applied to the common carotid artery. Over a 10-day period the clamp was intermittently screwed down, thus causing gradual occlusion of the lumen. No change was noted until, on the 11th day, one additional turn of the screw resulted in immediate coma on the

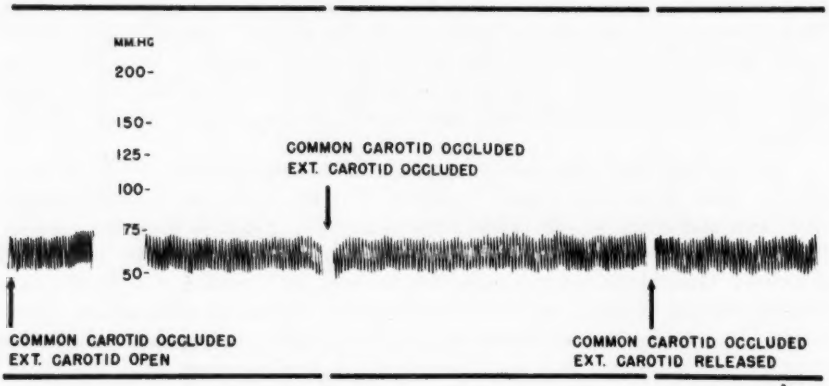

Fig. 1.—Intraluminal pressure changes in internal carotid artery, effect of associated occlusion of common and external carotid; based on studies by Sweet and Bennett on 13 patients with intracranial aneurysms.

part of the patient. Accordingly, the clamp was at once removed, removal restoring the artery to its original diameter. This situation is, of course, what should be expected in the light of the known dynamics of blood flow in relation to partial arterial occlusion. Mann and co-workers[17] have clearly shown that as an artery is progressively occluded, no change in blood flow occurs until the area of the lumen is decreased by 50%. A critical point is then reached, when small increments of occlusion will result in large diminutions of blood flow, so that an increase of 7% in occlusion (from 82% to 89%) may reduce flow by as much as 35%.

It is our opinion, then, that no method is currently available to make carotid artery ligation safe and that, in view of the high incidence of fatal, crippling, or unpleasant sequelae when this structure is ligated in the treatment of carotid body tumor, the procedure is unjustified without restoration of arterial continuity.

17. Mann, F. C.; Herrick, J. F.; Essex, H. E., and Baldes, E. J.: The Effect on the Blood Flow of Decreasing the Lumen of a Blood Vessel, Surgery **4**:249, 1938.

ARE CAROTID BODY TUMORS BENIGN OR MALIGNANT?

Much of the doubt and confusion that assail the surgeon attempting to remove a carotid body tumor stems from the fact that there is such divergence of opinion as to whether these tumors are benign or malignant. If a surgeon feels that he is dealing with a malignant tumor capable of killing the patient, he will justifiably be more aggressive in his operative removal, even at the expense of possibly damaging such an important structure as the carotid artery, with all its attendant serious sequelae.

In a laudable attempt to correlate and summarize important information on the various types of tumors which affect the human body, the Armed Forces Institute of Pathology, under the auspices of the Subcommittee on Oncology of the National Research Council, has recently published a fascicle on "Tumors of the Carotid Body" by Philip LeCompte.[18] This authority states as follows: "In view of the evidence summarized above that the great majority of these tumors are both clinically and histologically benign, it would seem doubtful whether anything more than a diagnostic biopsy should be done where tumors are without symptoms and growing slowly."

The contrary point of view is emphasized by Harrington, Clagett, and Dockerty,[19] who state: "Tumors of the carotid body are always malignant or potentially malignant." Lahey and Warren [20] say: "Malignancy when it does occur is of low grade. Local nodes are invaded but distant metastases suspected in a few cases have never been verified." Gratiot [21] states: "The incidence of malignancy in carotid body tumors is 15%-20%."

An attempt to evaluate the presence or absence of the malignant qualities of carotid body tumors based on histologic grounds alone is extremely precarious. We are inclined to agree with Frank Foote,[22] who says:

> Scarcely any pathologist at present has available to him sufficient material with long-term clinical follow-up to enable him to make trustworthy predictions of the clinical aggressiveness of any individual tumor. He may freely state that metastasis is a very remote and yet undocumented occurrence, but he must largely guess as to which tumor is likely to recur or to infiltrate adjacent tissues. Carotid body tumors are easily recognizable microscopically, but making the diagnosis of malignant versus nonmalignant carotid body tumors is a dubious venture.

As one sifts through the literature it becomes apparent that there is doubt about the capability of even the most proficient pathologist to lay down any histologic criteria that will permit one, on the basis of slide studies alone, to predict whether a tumor is benign or malignant. Since that is so, considerable aid in evaluating this point might be gained from observing the long-term clinical course of patients with

18. LeCompte, P. M.: Tumor of the Carotid Body and Related Structures (Chemoreceptor System), Armed Forces Institute of Pathology, Atlas of Tumor Pathology, Section IV, Fascicle 16, Washington, D. C., 1951.

19. Harrington, S. W.; Clagett, O. T., and Dockerty, M. B.: Tumors of the Carotid Body: Clinical and Pathological Considerations of Twenty Tumors Affecting Nineteen Patients (One Bilateral) Ann. Surg. **114**:820, 1941.

20. Lahey, F. H., and Warren, K. W.: Tumors of the Carotid Body, Surg., Gynec. & Obst. **85**:281, 1947.

21. Gratiot, J. H.: Carotid-Body Tumors: Collective Review, Internat. Abstr. Surg. **77**:177, 1943; in Surg., Gynec. & Obst. Sept. 1943.

22. Foote, F.: Personal communication to the authors.

untreated tumors. Unfortunately, there is a paucity of reports on such patients. Apparently, only infrequently has a surgeon been able to resist the attraction of attempted removal, or, if the tumors have been left untreated, accurate reports on their future behavior are not available.

From what long-term follow-up studies are available for analysis, the evidence supporting the contention that a significant percentage of carotid body tumors are malignant consists of reports on patients in whom recurrences at the local site have developed, resulting in death or serious disability. More convincing proof would consist of case reports in which the patient has died from distant dissemination of disease, apparently via the hematogenous route, with death from general carcinomatosis, as in cases of other malignant tumors. We shall present one such case.

Although a tumor recurs locally, this recurrence cannot be said to be conclusive evidence that the tumor is "malignant," as the term is usually employed in describing cancerous tumors. Nevertheless, if such local recurrences produce complications such as hemorrhage and death from continued local expansion and invasion, one must admit that the happening is distinctly disadvantageous to the patient and in the practical sense the tumor is fully "malignant." In our own series of cases no local recurrence has yet developed. However, as one surveys the literature on this topic one finds that recurrences have been reported by other authors and that the consequences of these recurrences have in some instances been fatal.

A partial survey of local recurrences of carotid body tumors reported in the literature which have resulted in death or serious complications to the patient follows:

In 1897, Middleton and Bierring [23] observed 43-year-old white man who had had a tumor for six months. The external carotid was ligated. No clinical diagnosis was made, but the pathological diagnosis was carotid body tumor. The patient recovered from the operation but had "paralysis of the palate." Recurrence took place two months later, and a tumor also appeared on the other side of the neck. Death occurred three months after operation. The text implies that death resulted directly from local tumor recurrence.

In 1904, Gilford and Davis [24] reported on a 52-year-old white man who had a tumor of three months' standing. The internal jugular was ligated, and the vagus and descendens hypoglossal nerves were injured. No clinical diagnosis was made; pathologically, the tumor was diagnosed as an "endothelioma." There was a recurrence in six weeks, and death occurred in five months. The text implies that death resulted from local tumor recurrence.

In 1906, Callison and Mackenty [25] observed a 53-year-old white man who had had a tumor for six years. The carotid artery was ligated. The pathological diagnosis was "mixed-cell sarcoma" of the carotid gland. The patient recovered from the operation but died from recurrence in eight months. The text implies that death resulted from local tumor recurrence.

23. Middleton and Bierring: Transactions Iowa State Medical Society Vol. 15, p. 94.

24. Gilford, H., and Davis, K. L. H.: Potato Tumours of the Neck and Their Origin as Endotheliomata of the Carotid Body, with an Account of 3 Cases, Practitioner **73**:729, 1904.

25. Callison, J. G., and Mackenty, J. E.: Tumors of the Carotid Body, Ann. Surg. **58**:740, 1913.

In 1909, Lilienthal [26] reported on a 38-year-old white woman who had had a tumor for 10 months. The first operation was only a biopsy; later one-half the tumor was removed. No clinical diagnosis was made, but the pathological diagnosis was perithelial hemangioma. The growth recurred, but there were no metastases. Death took place nine months later from repeated hemorrhage and cachexia.

In 1909, Douglas [27] reported on a 35-year-old white man who had a tumor of four months' duration. The external carotid was ligated during removal. The pathological diagnosis was malignant carotid gland tumor. There was prompt recurrence, and death occurred in four months. The text implies that death resulted from local tumor recurrence.

In 1913, Aperlo and Rossi [28] observed a 68-year-old white man who had had a tumor for three weeks. The internal jugular was ligated during removal. No clinical diagnosis was made, but the pathological diagnosis was carotid tumor. Recurrence took place in four months. The text implies that death resulted from local tumor recurrence.

In 1927, Duroux and Rollin [29] reported on a 48-year-old white man who had had a tumor for five months. No ligations were made (in this case the tumor was curetted out). No nerves were injured. No clinical diagnosis was made, but the pathological diagnosis was malignant tumor of the carotid gland. The patient recovered. Death occurred seven months later from local recurrence and general cachexia.

The position has been taken by some authors that many of these earlier reports were not adequately documented or that the entity of carotid body tumor was misdiagnosed and confused with metastatic carcinoma from a primary tumor within the oral cavity. We are not in a position to refute these charges completely, but on the basis of our own cases we think it is quite possible that at least some of the cases quoted may have been accurately evaluated, and we cannot escape the impression that if the patient is followed long enough the capabilities of this tumor to produce death or serious disability must definitely be granted.[30]

EVIDENCE SUPPORTING DISTANT DISSEMINATION OF CAROTID BODY TUMORS

Stronger evidence supporting the point of view that carotid body tumors may be malignant would exist in the form of cases in which distant metastases ultimately producing death had occurred. Although this possibility has been considered, its acceptance has been flatly rejected by some [18] and accepted only with reservations by others.[31] The literature does contain published case reports of such occurrences.

These cases may be classified into those in which distant dissemination has been limited to the cervical lymph nodes and those in which the tumor has spread apparently hematogenously to distant foci. In our own group we have one case (Case 4) of lymph node involvement. The node was located in the adjacent internal jugular group and was clearly separated from the primary tumor in such a way as to nullify

26. Lilienthal, H.: Endothelioma of the Carotid Body, Ann. Surg. **50**:808, 1909.

27. Douglas, J.: Perithelioma of the Carotid Gland, M. Rec. **75**:397, 1909.

28. Aperlo, G., and Rossi, F.: I tumori della ghiandola carotidea, Clin. chir. **30**: 26, 1927.

29. Duroux, E., and Rollin, L.: Contribution à l'étude des tumeurs de la glande carotidienne, Bull. méd. **41**:1107, 1927.

30. In addition to the cases cited, other local recurrences have been reported but until the time of the report no serious sequelae had been noted.

31. Lahey and Warren, footnotes 6 and 20.

any question of direct extension. Shawan and Owen,[32] Kopfstein,[33] Winship, Klopp, and Jenkins,[34] Lahey and Warren,[20] and Monro [35] have all reported single cases of metastases to adjacent cervical nodes. LeCompte [18] also includes such a case in his monograph but believes that the possibility of direct extension rather than metastasis had not been adequately ruled out. MacComb [9] reports two such cases that seem to satisfy all criteria.

Cases demonstrating widespread hematogenous dissemination are uncommon but not rare. Lattes and Waltner [36] have reported a case of glomus jugularis tumor culminating in death, and a large metastasis to the liver was demonstrated at autopsy. Although this tumor would not strictly qualify as a carotid body tumor, owing to its different location, the close histologic relationship of carotid body tumor and glomus juglaris tumor is well recognized. Donald and Crile [37] report a case in which at autopsy metastases to the fifth and sixth thoracic vertebrae were proved microscopically and there was x-ray evidence of bone lesions in the ribs, manubrium, and ilium. Goodof and Lischer [38] report a case in which death was due to aortic insufficiency and autopsy disclosed a tumor within the pancreas histologically similar to the carotid-body tumor. The possibility of this being a tumor *de novo* of multicentric origin and not a metastasis must be admitted. Pendergrass and Kirsh [39] report a case in which the first diagnosis was "angiosarcoma." The patient ultimately died from disseminated disease to the pelvis, femur, ribs, and sternum. The slides were reviewed in the light of the patient's subsequent clinical course, and a revised diagnosis of a malignant carotid body tumor was made. Murray Spotnitz [40] published a report concerning a carotid body tumor, terminating in death, with metastases to the cervical lymph nodes, skin of the chest wall, kidneys, pancreas, heart, and pleura. Grönberger [41] describes a case of single metastasis to one kidney and extension into the mediastinum, and Gilford and Davis [24] report one in which metastases to the liver were found at autopsy.

Undoubtedly most of the references mentioned have been reviewed by previous authors writing on this subject. By and large their acceptance has been questioned on the grounds that the text presentation was too brief or the photomicrographic reproductions were too limited or of too poor a quality. In some cases the photo-

32. Shawan, H. K., and Owen, C. I.: Carotid Body Tumors, Am. J. Surg. **40**:462, 1938.

33. Kopfstein, W.: Beitrag zur Kenntniss der Geschwülste der carotisdrüse Wien. klin. Rundschau **9**:83, 97, 117, 337, 356, 1895.

34. Winship, T.; Klopp, C. T., and Jenkins, W. H.: Glomus-Jugularis Tumors, Cancer **1**:441, 1948.

35. Monro, R. S.: The Natural History of Carotid Body Tumours and Their Diagnosis and Treatment With a Report of 5 Cases, Brit. J. Surg. **37**:445, 1950.

36. Lattes, R., and Waltner, J. G.: Nonchromaffin Paraganglioma of the Middle Ear (Carotid-Body-like Tumor; Glomus-Jugulare Tumor), Cancer **2**:447, 1949.

37. Donald, R. A., and Crile, G., Jr.: Tumors of the Carotid Body, Am. J. Surg. **75**:435, 1948.

38. Goodof, I. I., and Lischer, C. E.: Tumor of the Carotid Body and the Pancreas, Arch. Path. **35**:906, 1943.

39. Pendergrass, E. P., and Kirsh, D.: Roentgen Manifestations in the Skull of Metastatic Carotid Body Tumor (Paraganglioma), of Meningioma and of Mucocele: A Report of 3 Unusual Cases, Am. J. Roentgenol. **57**:417, 1947.

40. Spotnitz, M.: A Case of Malignant Tumor of the Carotid Body with Multiple Metastases, Oncologia **4**:239, 1951-1952.

41. Grönberger, G.: Ett fall av karotisköstel-tumör, Hygiea **79**:1669, 1917.

micrographic reproductions were adequate but their interpretation was challenged. We are in no better position than anyone else to clarify these points or refute such objections.

However, being well aware of the skepticism that has surrounded the question of possible dissemination of these tumors, we have gone to some pains to report in detail a case (Case 1) of our own which we believe satisfies all criteria. The pathological sections were circulated widely to leading pathologists in our country, and there has been no disagreement on the identity of the primary tumor and the distant foci, which include metastases to the heart, lungs, ribs, and vertebrae. The case will be reported separately [42] in a journal whose policy is better adapted to profuse documentation with many photomicrographs, including those showing special stains, but will be briefly reviewed here (Case 1 under "Report of Cases").

TREATMENT

It seems apparent to us that if nothing is done to interrupt the growth of these tumors, the patient sooner or later faces serious consequences as a result of either continued local growth or, in rare cases, distant dissemination. No spontaneous regression or cure has ever been reported. Similarly, all reports at control with radiation therapy remain unconvincing. No cure by this method has ever been claimed, and all statements to the effect that "regression" has been achieved or that "the tumor was held in check" with radiation therapy are equally unimpressive, since it is the very nature of this particular entity to remain in an apparently stationary condition or to grow only very slowly over a period of months or even years.

It is our considered opinion, therefore, that the tumor should be removed through surgical means. However, if we believed that surgical removal involved a mortality rate of 30 to 40%, as has sometimes been stated, we should not advocate such a step. Even though the tumor may have certain malignant potentialities, these have not been demonstrated to be so formidable as to justify carrying out a surgical procedure that entails so great an operative mortality. Our recommendation is based on the firm belief that it is possible to remove the carotid body tumor without interrupting the continuity of the arterial tree.

Gordon-Taylor [43] has expressed an opinion somewhat similar to ours, as follows:

> The main purpose of this communication is to plead once more for caution before undertaking a resection of the carotid bifurcation for a carotid tumor and to impress upon operators that even when the arteries appear almost imbedded in the growth, meticulous care and painstaking dissection may sometimes reveal a "white line" whereby the continuity of the main arterial vessels may remain undisturbed or at least structurally inviolate. The relatively advanced stage at which most of these cases come under the notice of a skilled observer imposes upon the surgeon the difficult decision between the maintenance of an intransigent respect for the integrity of the carotid bifurcation, and on the other hand, the prospect of an anxious, tedious piece of technique which awaits his execution if caution wisely prevails. Earlier operation would furnish a simple and safe exercise.

The embryological studies of Boyd [44] have shown that the carotid body itself originates in the adventitial layers of the artery. In the mature state, the carotid

42. Romanski, R.: Chemodectoma (Nonchromaffin Paraganglioma) of the Carotid Body with Distant Metastases: A Case Report, Am. J. Path., to be published.

43. Gordon-Taylor, G.: On Carotid Tumours, Brit. J. Surg. **28**:163, 1940.

44. Boyd, J. D.: The Development of the Human Carotid Body, Publication 152, Carnegie Institution of Washington 1937, Contrib. Embryol. **26**:1, 1937.

body maintains this relationship. Furthermore, tumors developing from the carotid body even in the most advanced state still preserve this relationship. Figures 2 and 3, taken from Boyd's studies, illustrate the definite confinement of the carotid body to the layers of the adventitia. Figure 4 is a photomicrograph taken from our most advanced case. Even in this case, in which the tumor had reached a sufficient size to fill the entire left neck and completely encase the vagus nerve, internal jugular vein, carotid artery, hypoglossal nerve, and glossopharnygeal nerve, microscopic studies revealed that the relationship of the tumor to the carotid artery still indicated that no actual invasion of the media by tumor was present. That is, although the lumen of this structure had been largely collapsed by extrinsic pressure, even in this case

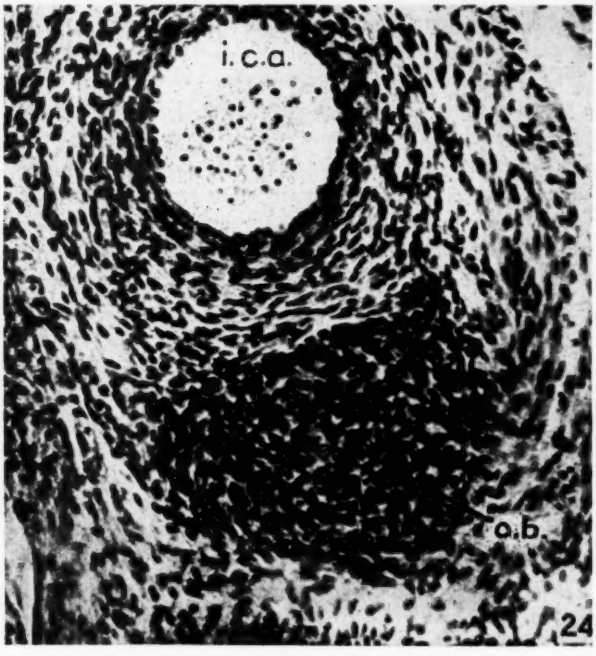

Fig. 2.—Transverse section of internal carotid artery in 32-mm. human embryo. Carotid body is separated from lumen of artery by definite tunica media and tunica adventitia. (From Boyd.[44])

it was theoretically possible to dissect off the tumor without entering either the tumor or the lumen of the artery. McSwain and Spencer's article [45] contains a photomicrograph which appears to show the relationship of a carotid body tumor to the adventitial layers. However, we disagree with their interpretation, at least as far as we are able to judge from this photographic reproduction, to the effect that invasion into the media had occurred.

The confinement of these tumors to the adventitial layers of the artery even in the advanced stage has an important bearing on attempts at operative removal. As

45. McSwain, B. and Spencer, F. C.: Carotid Body Tumor in Association with Carotid Sinus Syndrome: Report of 2 Cases, Surgery **22**:222, 1947.

a result of the vast experimental work on vascular surgery it has become apparent that it is the components of the media of the artery (elastic tissue and muscle) that contribute most of the tensile strength and prevention of leakage in arterial anastomoses and homografts.[46] Specifically, it is to be noted that not only does the adventitia of an artery contribute nothing to the success of anastomoses and homografts, but it is purposely dissected off and sacrificed. These embryological and histologic facts provide the fundamental explanation for our success in removing the tumor without damaging the artery in the last eight cases of our series.

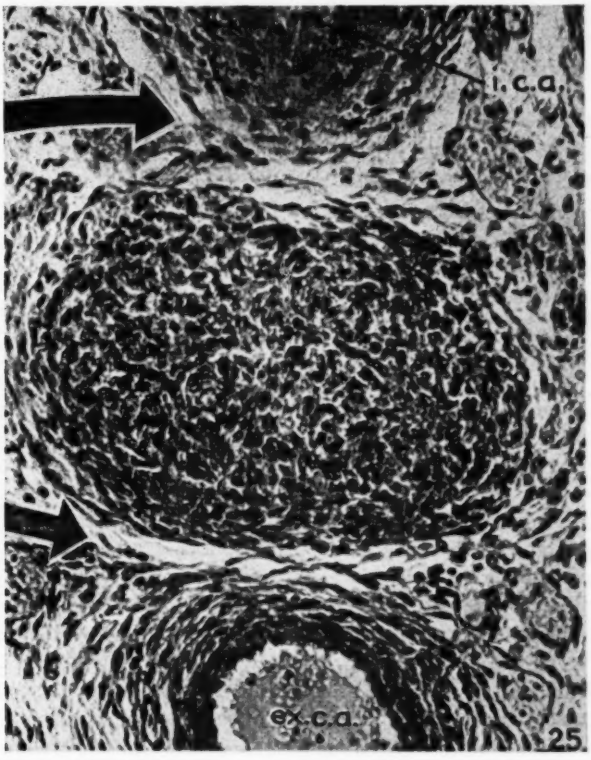

Fig. 3.—Transverse section of carotid body in 40-mm. human embryo. Confinement of carotid body to adventitia is well illustrated. This relationship is preserved in adult life even in presence of tumor formation. Arrows indicate desired plane of dissection in removing carotid body tumor. (From Boyd.[44])

After the exposure of the main arterial channels has been satisfactorily accomplished and safety tapes have been applied to the common, external, and internal carotid arteries, the dissection should start at some point away from the main body of the tumor itself in a plane calculated to be between the adventitia and the media of the artery. The objective should be to leave the media on the artery and strip

46. Swan, H.; Robertson, H. T., and Johnson, M. E.: Arterial Homografts: I. The Fate of Preserved Aortic Grafts in the Dog, Surg., Gynec. & Obst. **90**:568, 1950.

away all the overlying adventitia, and if this objective is accomplished the tumor will automatically be removed in the course of this achievement, since it is confined to the adventitia. The plane can be well delineated by injecting procaine (Novocaine) into the adventitia, and this injection has the additional advantage of nullifying any stimulus to the carotid sinus, with its attendant bradycardia that sometimes occurs. In Figures 2 and 4 this plane is indicated by the arrows.

It is the nature of carotid body tumors to be traversed throughout their entire substance with vascular channels. Some of these appear to have a connection with the lumen of the main artery proper and when cut across will bleed so briskly as to suggest to the inexperienced that the worst has happened and that a hole in the lumen of the carotid artery now exists. This annoying complication can be controlled with figure-of-eight transfixion arterial sutures. Traction on the safety tapes during the obliteration of these pinpoint arterial connections will produce temporary control of the bleeding while the suturing is being carried out.

If one should actually damage the main arterial trunk, what procedure should then be followed? To settle at this stage for ligation of all major arterial trunks should never be done. Many times it has been possible to sew up the hole in the artery with satisfactory results. If this procedure should prove impossible, a primary anastomosis between the internal carotid artery and the common carotid artery should then be considered. Enderlen [47] carried out this procedure in one case in 1913, and in the same year Schmidt [48] duplicated it with apparent success.

In the event neither of these possibilities is possible, either a stored arterial homograft or a freshly obtained venous autograft should be inserted. In all these schemes it must be borne in mind that time is of the essence in restoring the blood flow through the arterial stem. We have had on our desk for several years an apparatus designed to permit us to insert an arterial homograft into a large carotid defect while at the same time maintaining blood flow through a polyethylene shunt while the anastomosis is carried out. Although we have constantly been on the watch for a suitable case in which to employ this apparatus, in connection with not only carotid body tumors but other forms of head and neck cancer, we have never yet encountered a case in which we found its use imperative.

The postoperative care is routine. If one chooses to take the opportunity to inject procaine hydrochloride into the stellate ganglion, the injection can be done without any difficulty. We are not believers in the postoperative use of heparin in such cases, since we feel that if one were to survey all the difficulties and postoperative complications resulting from the use of heparin, one would probably be able to compile information indicating that the total aggregate harm done by this adjunctive procedure probably exceeds its proved benefit.

If one should be dealing with a malignant carotid body tumor it must be admitted that peeling the tumor off with such a narrow margin as that described may leave the way open to future local recurrences. Our studies indicate, however, that there is a well-defined capsule around most of these tumors and that if one carries out the dissection in the plane between the adventitia and the media of the artery, this capsule will not be perforated and the tumor will be removed *in toto*. The accuracy

47. Enderlen: Demonstrationen, abstracted, Beitr. klin. Chir. **83**:726, 1913.

48. Schmidt, J. E.: Beiträge zur Kenntnis der Glandula carotica und ihrer Tumoren, Beitr. klin Chir. **88**:301, 1913.

of such a viewpoint can be evaluated only in the light of long-term follow-up on patients on whom this operation has been carried out. For the moment, on the basis of all available evidence, it seems to us better to remove the tumor in this fashion and preserve the continuity of the carotid arteries than to sacrifice the latter structures in order to gain a wider margin.

REPORT OF CASES

During the period 1938-1952 a total of 12 patients with carotid body tumors have come under our care at the Bonfils Tumor Clinic. The tumors were removed in all but one instance, and in 8 of the 11 cases of resection this was accomplished without interrupting the continuity of the arterial stream. In the three cases in which ligation was carried out no permanent sequelae developed. There were no deaths from the operative procedures, but one patient died from recurrent disease. The follow-up studies cover a period varying from 14 years to several months. Local recurrence associated with distant dissemination of the disease culminating in death developed in one instance. Metastases to the regional cervical nodes occurred in one case, but the patient had had no further difficulty six years after local removal of the primary tumor coupled with a rather limited dissection of the grossly involved nodes. No recurrences have appeared in any of the other patients.

CASE 1.—*History.*—A. R., a 53-year-old white man, was first seen in the Bonfils Tumor Clinic June 14, 1943. He was referred by his local physician, who had excised a lump from from the neck, left. A gross diagnosis of "carcinoma" had been made by his physician, and the request was made that he be given x-ray therapy. At this time the left tonsil was found to be displaced medially, apparently from extrinsic pressure, and there was a diffuse swelling in the lateral pharyngeal wall. A biopsy specimen was taken from the pharyngeal wall but was reported as negative. The tumor mass was described by the examiner on the original admission as being fixed to underlying structures and was considered inoperable.

Irradiation was begun to the left cervical region, and a total of 300 r times 12 was given, with 220 kvp, a target-to-skin distance of 50 cm., and 0.5 mm. copper filtration. There was some regression in size, but the mass never completely disappeared. In 1946 obvious recurrence had taken place and the patient had become hoarse. Examination revealed hoarseness to be due to left laryngeal paralysis. A biopsy of the neck mass was done in 1949 and the specimen reported as radiation fibrosis. The mass continued to become larger and more fixed to surrounding structures. In June, 1950, the patient was again seen in the follow-up clinic.

Examination.—A large mass with indefinite borders occupied the greater portion of the left neck. There was much fibrosis and scarring from the previous biopsy and radiation therapy. Intraoral examination was negative. On June 20 biopsy was repeated, and for the first time a definite diagnosis of carotid body tumor was obtained. Paralysis of the larynx and the left side of the tongue indicated an infiltrating tumor mass. Chest plates were negative.

Operation.—On July 3 removal of the tumor necessitated an operation approaching a radical neck dissection. No attempt was made to preserve the carotid artery, inasmuch as the preoperative examination had indicated vagus and hypoglossal invasion and the assumption was therefore made that the carotid artery was also occluded with tumor. Once sacrifice of these structures had been decided upon, no difficulty in removing the mass was encountered until the region of the base of the skull was approached. At this point no clear-cut upper margin could be demonstrated. The internal carotid artery, the internal jugular vein, and the spinal accessory, vagus, and hypoglossal nerves were all sacrificed at the level of the base of the skull, and the tumor was lifted out. A skin graft was necessary to complete closure.

The postoperative course was complicated by intermittent difficulty in swallowing, which persisted until the patient's death. Despite his difficulties, there were periods when he apparently could handle food normally. This ability could not be relied upon, however, and he was therefore discharged with a tracheostomy tube in situ and with primary reliance on a nasal tube for feeding.

Follow-Up.—The patient remained more or less invalided from this point on. A chest plate repeated four months after operation revealed for the first time opacities suggestive of metastases. He began to lose weight gradually and was entirely dependent on the tracheostomy tube for respiration. He was admitted once more to the hospital, for a thorough investigation as to whether the cause of his general downward path was not simple nutritional deficiency. He rallied somewhat under high-caloric forced feedings but never was restored to good health. On May 14,

Fig. 4.—Cross-section of junction of carotid body tumor and internal carotid artery, Case 1. Top arrow indicates tumor; middle arrow, plane of dissection, and bottom arrow, media. Note preservation of relationship of tumor to media even in this advanced stage. Although complete encirclement of artery by tumor was present, necessitating sacrifice of artery, no infiltration into lumen had occurred.

1952, he was admitted to the hospital after an episode of hemoptysis. His course during the interim had been marked by progressive increase in the size of the lung opacities, together with the appearance of new lesions throughout the lungs, veterbrae, and ribs. Pain on motion developed with the onset of these lesions. He continued to cough up bright-red blood and died 24 hours after admission, the immediate cause of death being uncontrolled pulmonary hemorrhage.

Autopsy Findings.—A thorough autopsy was carried out and confirmed the clinical diagnosis of recurrent carotid body tumor, and abundant microscopic sections were made of the lung, heart, and bone lesions. All these were similar in their histologic pattern, and nothing was discovered which forced us to change our clinical impression that the carotid body tumor had disseminated widely throughout the body. The immediate cause of death was the erosion into the bronchus of one of the pulmonary metastases, with resultant ulceration and hemorrhage. Since we were aware of the fact that previously reported cases had been accepted with some skepticism, a particular effort was made to do a thorough autopsy, make numerous slides, and circulate these to a number of pathologists. We were pleased to find that, at least on this one occasion, no pathologist seemed to differ with any of his colleagues, and unanimous agreement on the diagnosis was obtained.

Fig. 5.—Autopsy specimen of heart, Case 1. Metastasis to heart is shown. Other metastases to lungs, vertebrae, and ribs were proved histologically. Carotid body tumors cannot be considered harmless but are dangerous or fatal from either continued local growth or distant dissemination in a significant proportion of cases.

CASE 2.—*History.*—A. S., a 28-year-old white woman, was admitted to Colorado General Hospital on Jan. 27, 1938, with an initial diagnosis of an aneurysm in the carotid artery. She had complained of swelling of the right neck for three years, with a gradual increase in size. In the year prior to her admission, pain radiating to the ear and parietal region associated with headache had appeared with increasing frequency. Tonsillectomy had been performed when the mass was first noted, on the assumption that the cervical lymph nodes were enlarged secondarily to tonsillar infection.

Examination.—A tumor measuring 6 by 3.5 cm. and described as "fluctuant and pulsating" was present. Other signs found in association with arteriovenous aneurysms such as a to-and-fro murmur and bradycardia on pressure over the mass, with disappearance of the murmur on occlusion of the carotid artery, were reported. Daily compression of the common carotid artery was begun, and pressure was increased until occlusion for 10 minutes was achieved.

Operation.—On Feb. 18 the mass was explored, and the right common carotid artery was ligated. It was the plan at this time to remove the tumor in two stages. After ligation of the carotid artery the patient recovered without sequelae, and the tumor mass decreased in size. One month later a second operation was done, and the tumor was removed, triple ligation being carried out. Recovery again was uneventful, and the diagnosis of carotid body tumor was confirmed microscopically.

Follow-Up.—There had been no recurrence of disease 14 years after surgery.

CASE 3.—*History.*—S. N., a 12-year-old white girl (included through the courtesy of Dr. John M. Foster), was admitted to the hospital on Sept. 25, 1946, with a history of a mass on the left side of the neck of three months' duration. A diagnosis of tuberculous adenitis had been suspected, since there was a history of tuberculosis in the family. Four x-ray treatments directed at the mass produced no results. This patient is the youngest we have encountered either in our own practice or upon review of the literature.

Operation.—Sept. 26 the mass was removed, with preservation of the common and internal carotid arteries. Convalescence was uneventful. A diagnosis of carotid body tumor was confirmed by pathological examination.

Follow-Up.—No evidence of recurrent disease had appeared six years postoperatively.

CASE 4.—*History.*—T. J. A., a 35-year-old woman (included through the courtesy of Dr. John Hedrick), was seen on Jan. 22, 1947, with a history of a mass in the left submaxilliary area that had been present for 10 to 15 years. There had been a gradual increase in size during the two years prior to admission.

Examination.—The intraoral examination was negative. The 3 by 3 cm. mass was described as firm and nontender and located in the approximate region of the bifurcation of the carotid. There was a marked transmission of carotid pulse, although the mass was not felt to be expansile or compressible. The preoperative diagnosis was metastatic thyroid cancer, although no definite tumor was palpated in the thyroid area.

Operation.—On Jan. 22 the mass was removed. Triple ligation of the carotid fork was executed. During the course of exposure of the tumor several of the internal jugular lymph nodes were removed. An unexpected finding by the pathologist was a metastasis to one of these cervical lymph nodes.

After surgery the patient had a rough time and suffered from hemiplegia and a complete aphasia. These conditions gradually cleared, and at the end of 12 months no aftermath persisted.

Follow-Up.—There had been no recurrence of tumor five to six years after operation.

CASE 5.—*History.*—E. G., a 57-year-old white woman, was first seen in the Bonfils Tumor Clinic Nov. 26, 1949, with a mass in the right side of the neck of two years duration. The patient associated this mass with an attack of lobar pneumonia which she claimed cleared but left "the lump in the neck." There was a slow increase in size, and the patient had had a tonsillectomy and adenoidectomy again because of the assumption that the neck mass was due to bad tonsils. In the few months prior to admission some difficulty in swallowing had appeared.

Examination.—A 4 by 4 cm. firm nontender mass was noted. Intraoral examination failed to reveal any sign of a primary tumor.

Operation.—On March 10, 1950, a tumor lying in the bifurcation of the carotid artery was dissected free of the vessels and removed *in toto*. Convalescence was without sequelae. Pathological examination confirmed the clinical diagnosis.

Follow-up.—There had been no recurrence 2 years and 10 months after operation.

CASE 6.—*History.*—A 78-year-old white man was first seen in the Bonfils Tumor Clinic June 1, 1950. He complained of a mass in the left neck, which he stated had been present for eight years, with enlargement and pain in the last six months. Some difficulty was encountered in swallowing. In the few months prior to admission he had also begun to experience a dull pain in the left eye and left side of the head and reported that the mass had doubled in size.

Examination.—A 3 by 3 cm. firm, smooth mass located at the level of the carotid bifurcation was noted. It was said to move readily in a transverse plane but not in a vertical plane.

On auscultation, no thrill was heard, although the pulsations of the carotid artery were well transmitted. The mass decreased in size upon carotid compression, and at one examination bradycardia culminating in syncope was produced. Intraoral examination was negative. A preliminary diagnosis of carotid body tumor was made.

Operation.—On July 8 the tumor was found nestled in the bifurcation of the left carotid artery. The common carotid was mobilized below the mass and the internal and external carotid arteries above. Safety tapes were placed around these structures, and the external carotid was ligated and divided. The typical vascularity was encountered during the dissection, but the tumor was successfully separated from the artery in the adventitial plane. At one point during manipulation of the carotid artery there was a marked fall in blood pressure, which was immediately relieved upon release of one of the tension ligatures.

Convalescence was essentially uneventful, and the clinical diagnosis was confirmed by pathological study.

Follow-up.—No recurrence had occurred two and one-half years postoperatively.

CASE 7.—*History.*—G. E., a 37-year-old white woman, in August, 1950, was referred with the following history: Nine years prior to admission she had noted a lump in her right neck. One year previously she began to have pain associated with an increase in the size of this mass. She applied to a well-known clinic, where an attempt to excise the mass during local anesthesia was made. The surgeon informed her that he had found a carotid body tumor and that because of the danger associated with removal and the recognized benign course of such tumors, he had elected to leave it alone. No biopsy specimen was obtained.

The patient was not satisfied with this decision and continued to worry about the mass. In addition she felt that her pain had increased and that there was beginning difficulty in moving the tongue. After a discussion with her concerning the possible necessity of ligating the carotid artery, with the resultant ill effects, she decided to defer any further operative attempt "until her children had grown up."

She was seen on three subsequent occasions, each time stating that her pain was gradually increasing, and as far as could be determined by objective examination the mass was gradually increasing in size. On a trip to a southern surgical clinic this mass was successfully removed without interruption of the carotid stream.

Follow-up.—There has been no recurrence of tumor to date, and the patient is relieved of the mental worry associated with the existence of the mass.

CASE 8.—*History.*—M. A., a 68-year-old white woman, was first seen in the Bonfils Tumor Clinic Jan. 15, 1952. She complained of a tumor mass in the left side of the neck of seven years' duration. There was little or no change in the character of the mass during this time. She had been prompted to seek medical care concerning this mass primarily because of cancer propaganda.

Examination.—A mass measuring 4 by 5 cm. located in the mid-portion of the left neck was noted. The oral and pharyngeal cavities were normal. An aspiration biopsy was performed, but only blood was obtained. A preoperative diagnosis of a tumor of the submaxillary salivary gland was made.

Operation.—In February the tumor was found to be a carotid body tumor. During the course of removal a hole was torn in the carotid bulb and a portion of the internal carotid artery. This was closed primarily with arterial sutures, although an arterial homograft was ready for insertion should this procedure fail. The hypoglossal nerve was closely associated with the tumor and was freed with some difficulty.

The postoperative course was uneventful except for some temporary paralysis of the left side of the tongue. The clinical diagnosis was confirmed in the laboratory.

Follow-up.—There had been no recurrence of the tumor one year postoperatively.

CASE 9.—*History.*—C. S., a 69-year-old white woman, had been a patient in the psychopathic hospital since 1916, with a diagnosis of dementia praecox and epilepsy. The ward psychiatrist noted a mass in the left neck in January, 1952, and referred the patient to the surgery clinic for evaluation.

Examination.—A mass estimated at 6 cm. in diameter was located anterior to the sternocleidomastoid muscle at the level of the carotid bifurcation. Search for a primary tumor in the oral cavity was negative. No other masses were noted. The mass was soft, suggesting a cyst.

Operation.—The mass was excised on Feb. 26 without sacrificing the carotid artery. Recovery was uneventful. Pathological confirmation of the diagnosis of carotid body tumor was obtained.

Follow-up.—There had been no recurrence of disease one year after operation.

CASE 10.—*History.*—M. G., a 54-year-old Negro woman with a history of a mass in the right neck of one year's duration, reported to the Bonfils Tumor Clinic on March 16, 1952. The mass had been diagnosed by one physician as mumps, and no treatment was recommended. In the three months immediately prior to admission the right lateral pharyngeal wall had bulged medially to such an extent that she was having difficulty eating solids and had shifted to soft and liquid foods. No pain or other associated symptoms were present.

Examination.—The right tonsil was markedly enlarged and was covered with an intact mucosa at all points. The remaining portion of the right lateral pharyngeal wall bulged medially, and the impression was that the swelling was due primarily to a large tonsillar mass which was distorting the adjacent tissues. In the right neck a mass measuring 4 by 6 cm. was noted. It was the impression of the examiner that the patient had a primary lymphosarcoma of the right tonsil with metastases to the cervical lymph nodes. An aspiration biopsy was unsuccessful.

Operation.—On July 14 the mass was explored, and a large carotid body tumor was encountered. Although it was possible to preserve the common and internal carotid arteries, the vagus and hypoglossal nerves appeared to be completely surrounded with tumor. A decision was made to sacrifice the latter two structures in order to gain a complete removal of the mass. The diagnosis of carotid body tumor was confirmed by pathological examination.

A tracheostomy was performed at the conclusion of the operation, since it was felt highly likely that the surgery together with the unilateral paralysis might well result in sufficient edema to obstruct the airway. This assumption proved correct, inasmuch as the patient was dependent on the tracheostomy tube for approximately two months postoperatively. It was then removed without any sequelae.

Considerable difficulty swallowing food was encountered in the postoperative period and was severe enough to necessitate regular feedings with a nasogastric tube. The patient became adept at passing this and was discharged from the hospital with a good blendor with which she was able to maintain adequate nutrition. This situation prevailed for approximately four months after her operation, after which time she regained her ability to swallow without aspiration and returned to normal ingestion habits.

Follow-up.—There had been no recurrence seven months postoperatively. There is residual unilateral paralysis of the tongue and larynx, which is expected to be a permanent residuum of the operation.

CASE 11.—*History.*—N. C., a 60-year-old white woman, was referred on Aug. 18, 1952, with a right neck mass which she stated was of only four weeks' duration. There were no associated symptoms.

Examination.—Intraoral examination was negative. The mass itself measured 3 by 3 cm. and was rather soft and cystic in consistency. An aspiration biopsy was attempted, but only blood was obtained.

Operation.—On Aug. 20 the patient was operated on and a carotid body tumor was found. It was removed without sacrificing the continuity of the carotid stream. The hypoglossal nerve was traumatized during the course of this dissection but not divided. The postoperative course was uneventful.

Follow-up.—There had been no recurrence 10 months after operation.

CASE 12.—*History.*—E. L., a 50-year-old white woman, was referred in October, 1952, with the complaint of a left neck mass of two years' duration. There was no mention of pain, tenderness, or disability of any type.

Examination.—In the left neck beneath the angle of the jaw and lying for the most part anterior to the sternocleidomastoid muscle but partly covered by it was a soft mass measuring 3 by 3 cm. The consistency of the mass suggested cyst formation. Attempts to demonstrate lateral motion and perpendicular fixation were not helpful. A search of the base of the tongue, hypopharynx, nasopharynx, and adjacent structures was unproductive. An aspiration biopsy was attempted but only blood was obtained.

Operation.—On Nov. 28 the patient was operated upon. A curved incision overlying the dome of the mass was made. As the exploration continued, a tumor mass lodged in the bifurcation and having all the gross characteristics of a carotid body tumor was visualized.

An extension to the skin incision was then made. The carotid sheath was entered, and a rubber tissue drain was looped around the common carotid artery. Armed with the confidence, based on previous cases, that the tumor was removable without interruption of the carotid artery, the operator used fine forceps to develop a plane in the adventitia of the artery, and the dissection was directed centrally toward the mass itself in this plane. Mobilization from the lateral and posterior walls of the artery was accomplished with no difficulty. The external carotid artery was then divided, and the mass was swung laterally, facilitating exposure for further dissection on the medial side of the bifurcation and internal carotid artery. Bleeding continued to be profuse, and replacement with transfusion was provided. The tedious and painstaking dissection progressed, and the tumor was successfully mobilized free of the main arterial vessels.

At the time of exposure the mass measured 4 by 4 cm. As the mobilization proceeded and the afferent blood supply diminished, the mass gradually collapsed, so that upon complete removal its dimensions did not exceed 3 by 3 cm. Recovery was uneventful, and confirmation of the clinical diagnosis was obtained by pathological study.

Follow-up.—There had been no recurrence five months postoperatively.

SUMMARY AND CONCLUSIONS

A survey of the literature on carotid body tumors with particular reference to the incidence of local recurrences, regional spread, and distant dissemination has been made. The conclusion has been drawn from this survey together with the experience based on 12 cases reported from our clinic that carotid body tumors may be expected to cause serious trouble through continued local growth, regional lymphatic spread, or distant dissemination in a significant proportion of cases. In view of these conclusions the surgical removal of carotid body tumors is recommended.

Embryological studies of the carotid body have shown that this structure arises in the adventitia of the carotid body and that this relationship is maintained in adult life. Furthermore, tumors arising from the carotid body maintain this relationship as well. The adventitia of large and medium-sized arteries can be sacrificed without compromising the success of primary anastomosis or arterial homografts. When these tumors are operated upon reasonably early they may be safely and completely removed without interrupting the continuity of the arterial stream if the dissection is carried out in the plane of the arterial adventitia.

In the event that the lumen of the artery is inadvertently entered in the course of removal, ligation should never be resorted to, because there is no method by which such a step can be made safe for the patient, regardless of any preoperative or postoperative adjunctive measures. Restoration of continuity of the arterial stream by means of simple closure of the hole, primary end-to-end anastomosis, and insertion of an arterial homograft or venous autograft are recommended in that order as a solution to this complication.

DISCUSSION

On Papers by Drs. Crabtree and Hunter, Drs. Meckstroth and Curtis, and Drs. Morfit, Swan, and Taylor

Dr. Henry K. Ransom, Ann Arbor, Mich.: A survey of the literature pertaining to diseases of the thyroid gland during the past several years reveals that much emphasis has been placed upon the nontoxic solitary nodule as a particularly dangerous lesion with respect to the incidence of malignant growth.

Our experience has been similar to that of Beahrs, Pemberton, and Black,[1] of the Mayo Clinic, who stated:

"There was little agreement among physicians who had examined the patient as to whether there was a single mass or multiple nodules within the thyroid gland. There was, in addition, little agreement between the clinical findings and the pathologist's report. In cases in which several examiners agreed that the nodule was single, examination of the surgical specimen, more usually than not, revealed multiple adenomas. In our experience, a truly solitary nodule is rather unusual, as are cases in which the pathologic changes are limited to one region of the thyroid."

[Slide] Lange and MacLean,[2] at the University Hospital, Ann Arbor, Mich., in 1949, from a review of the surgical material in 1,326 cases of thyroidectomy, compared the clinical observations and the operative and pathologic findings. Their data are given in the accompanying Table.

It will be noted that frequently nodules were found at operations which had not been detected on clinical examination but, most importantly, that the clinical diagnosis of a solitary nodule was ultimately proved to be correct in only 19.5% of the cases. One must conclude therefore that the term "solitary" or "discrete" adenoma is to be regarded as a clinical diagnosis only and that it often fails to denote the true pathologic state.

Group I	Clinically palpable nodular goiter		836
	Multinodular	677	
	Multiple nodules	641	
	Single nodule	1	
	No nodules found	35	
	Single nodule	159	
	Single nodule	31	
	Multiple nodules	126	
	No nodules	2	
Group II	Clinically palpable diffuse goiter		444
	No nodules	317	
	Multiple nodules	123	
	Single nodule	4	
Group III	Clinically nonpalpable goiter		46
	No nodules found	30	
	Multiple nodules	16	

While there is abundant evidence in the literature to indicate that patients who exhibit a solitary nodule will show a higher incidence of carcinoma than those with multinodular goiters, the incidence of 7.26% in glands with multiple nodules is a matter for concern. In cases with multiple adenomas, carcinoma may originate in a small adenoma as often as in a large one, and, furthermore, not infrequently, cancers of multicentric origin are found.

It is our belief that thyroid adenomas are benign neoplasms, and in their studies, Crabtree and Hunter have convincingly demonstrated the sequence of adenomas with atypical proliferation to early carcinoma in an adenoma, and thence to the more invasive forms of cancer in which penetration of the capsule has taken place.

In spite of the tendency at present to adopt a complacent attitude toward multinodular goiter and to emphasize the solitary adenoma as the most formidable precancerous lesion, we believe that, barring general contraindications, thyroidectomy should be advised in all cases of adenomatous or nodular goiter, because of the high incidence of unusupected malignant growth, and also because of the cancer potentialities of benign thyroid adenomas. Frequently the indications for removal are multiple, since pressure symptoms, toxicity, and cosmetic reasons may be coexistent.

1. Beahrs, O. H.; Pemberton, J. de J., and Black, B. M.: Nodular Goiter and Malignant Lesions of the Thyroid Gland, J. Clin. Endocrinol. **11**:1157, 1951.

2. Lange, H. J., and MacLean, K. F.: Malignant Neoplasms of the Thyroid, Surgery **26**:862, 1949.

COMBINED OPERATIONS FOR INTRAORAL AND LARYNGEAL CARCINOMA

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THE MANAGEMENT of intraoral and laryngeal malignant lesions and of metastatic tumors produced by these lesions has been fraught with constant effort to improve a discouraging situation in which, paradoxically, a relatively low rate of cure has been obtained in spite of the fact that widespread metastasis is uncommon even in the later stages of these diseases.[1]

HISTORICAL REVIEW

According to Butlin and Spencer,[2] excision for cancer of the mouth was practiced in the 16th century and even earlier, but utilization of cautery in some form or other was the usual method of treating malignant disease in this region. Excision had been performed frequently enough so that Harris,[3] in a lecture to the Royal College of Physicians on Oct. 7, 1720, said:

> The excision of cancers of the mouth and lips, and especially of the tongue, all involve the greatest danger to life. But if anyone is exceedingly wearied with such tumours, and especially dejected in mind, whilst he is prepared to bear equably whatever may happen, he should not be denied the trial of the operation of excision.

He went on to tell how a kindly neighbor of his, who had neglected treatment, called in a famous surgeon, who at once persuaded the patient to have a cancer of the tongue excised. It turned out that the surgeon had lost both his previous patients.

> A few days afterwards this case also went to the majority, and joined the two preceding ones in misfortune, whence no one ever returns to overcome the malpraxis of ignorant physicians and of rash surgeons.

Read at the Tenth Annual Meeting of the Central Surgical Association, Chicago, March 6, 1953.

From the Division of Surgery (Dr. Beahrs) and the Section of Plastic Surgery (Dr. Devine) of the Mayo Clinic. Dr. Pemberton is a Fellow in Surgery, Mayo Foundation.

1. (*a*) Martin, H.: The Treatment of Cervical Metastatic Cancer, Ann. Surg. **114**:972-985 (Dec.) 1941. (*b*) Martin, H. E., and Sugarbaker, E. D.: Cancer of the Floor of the Mouth, Surg., Gynec. & Obst. **71**:347-359 (Sept.) 1940. (*c*) Martin, H.; Del Valle, B.; Ehrlich, H., and Cahan, W. G.: Neck Dissection, Cancer **4**:441-499 (May) 1951. (*d*) Slaughter, D. P.: Neck Dissections: Indications and Technics, S. Clin. North America **26**:102-115 (Feb.) 1946.

2. Butlin, H. T., and Spencer, W. G.: Diseases of the Tongue, Ed. 2, London, Cassell & Co. Ltd., 1900.

3. Harris, W., cited by Butlin and Spencer,[2] p. 353

C. J. M. Langenbeck,[4] in 1819, was one of the earlier physicians to initiate and advance operative technics on the tongue by the introduction of the wedge-shaped operation and closure of the defect with sutures. In 1827, Major [5] split the tongue down the center and applied ligatures to the diseased tongue through the mouth. In 1831, Jaeger [6] was the first to split the cheek to gain access to the tongue and to make more room for the excision of intraoral growths. Roux,[7] in 1836, was the first to describe a major operation such as might be carried out at the present time for the removal of intraoral carcinoma. He is given credit for splitting the lower lip and sectioning the mandible to gain access to intraoral carcinoma. Syme,[8] in 1857, and Billroth,[9] in 1861, described similar procedures.

About 1861, B. von Langenbeck [10] was recommending resection of the mandible not only to gain access to lesions within the mouth but to do an adequate operation for cancer if the tumor involved or was intimately associated with the mandible. Bloodgood [11] was one of the earliest surgeons to advocate a limited mandibulectomy, together with excision of the intraoral lesion. He also performed a modified dissection of the upper part of the cervical region.

In 1877, Whitehead [12] systematized the intraoral technics for surgical excision of carcinoma. Kocher,[13] in 1880, systematized the submaxillary approach to cancer of the tongue and stressed the importance of removal of cervical lymph nodes. The technics of these two men were developed from the experience gained by surgeons from the time of C. J. M. Langenbeck.

In 1900, Butlin and Spencer [2] stressed the importance of the cervical lymph nodes in the treatment of any intraoral carcinoma. After Crile,[14] in 1906, proposed and developed what is known today as "radical neck dissection," the treatment of intraoral carcinoma and its cervical metastatic lesions was separated into irradiation for the former and radical dissection of the neck or irradiation for the latter. Results of these methods were not much better than those obtained by earlier methods of treatment, although the operative mortality was less. More discouraging was the grave prognostic significance of involvement of the mandible.

In the early part of the present century, the operative mortality rates for intraoral malignant disease, especially for lesions of the tongue, were about 7% when the operation was strictly intraoral, 20% when the upper cervical nodes and the intraoral tumor were resected at the same operation, and 25% when the jaw was sectioned.[2] Hemorrhage, shock, infection, and pneumonia were the causes of death.

4. Langenbeck, C. J. M., cited by Butlin and Spencer,[2] p. 355
5. Major, cited by Butlin and Spencer,[2] p. 355
6. Jaeger, cited by Butlin and Spencer,[2] p. 356
7. Roux, cited by Butlin and Spencer,[2] p. 359
8. Syme, Cited by Butlin and Spencer,[2] p. 360.
9. Billroth, cited by Butlin and Spencer, [2] p. 365
10. von Langenbeck, B., cited by Butlin and Spencer,[2] p. 365.
11. Bloodgood, J. C.: Lesions of the Oral Cavity and of the Jaws and the Region of the Jaws, Including the Temporal Fossa, Orbital Cavity, and Sinuses, in Practice of Surgery, edited by D. Lewis, and W. Walters, Hagerstown, Md., W. F. Prior Company, Inc., 1952, Vol. 4, pp. 1-280.
12. Whitehead, cited by Butlin and Spencer,[2] p. 364.
13. Kocher, cited by Butlin and Spencer,[2] p. 365.
14. Crile, G.: Excision of Cancer of the Head and Neck, with Special Reference to the Plan of Dissection Based on 132 Operations, J. A. M. A. **47**:1780-1786 (Dec. 1) 1906.

At about this time, the radiologist appeared on the scene. He could treat malignant disease without an operation and with a mortality rate lower than that of operative procedures. For about 30 years the radiologist treated the larger share of patients who had such lesions. Although high hopes were held for this method, the results remained discouraging.

With development of better understanding of the basic principles of surgical technics for removal of cancer, namely excision of the primary lesion, the intervening lymphatic vessels, and the regional lymph nodes, or "excision and dissection in continuity," as exemplified by the perfection of modern procedures for radical mastectomy and combined abdominoperineal resection, a reevaluation of the treatment of intraoral malignant lesions was undertaken. It became apparent that nowhere in the body could the concept of excision and dissection in continuity be applied with sounder logic, since intraoral malignant lesions display little tendency to invade the veins and produce distant metastatic lesions but tend to confine themselves to lymphatic extension above the clavicle, where complete excision should be a reasonable possibility. In addition, the anatomic contributions by Pólya and Navratil,[15] in 1902, which demonstrated that in 50% of persons the lymphatic vessels of the tongue and floor of the mouth pass through the periosteum of the mandible on their way to the upper cervical nodes, were reviewed and applied to the treatment of intraoral malignant disease. It was realized that removal of the primary lesion in the mouth followed by dissection of the neck completely ignored the region of the floor of the mouth and mandible, through which malignant cells can pass to reach the cervical nodes.[16]

With the advent of modern technics in anesthesia, improved preoperative and postoperative care, including correction of imbalances in proteins, fluids, and electrolytes, and the introduction of modern chemotherapy, it remained only for Martin and associates [1c] and others [17] to apply these principles to the treatment of intraoral malignant lesions and to standardize operative technics.

Until recently, the presence of bilateral cervical metastatic lesions was considered a contraindication to radical dissection of the neck, although this procedure had been performed occasionally as far back as the turn of the century by Duval,[18] Ewald,[18] Dangel, [18] and Crile,[14] with varying results in regard to operative mortality. Sugarbaker and Wiley [21] were of the opinion that the increase in pressure of the cerebrospinal fluid encountered immediately after ligation of the second internal

15. Pólya, A. E., and Navratil, D., cited by Ward and Robben, Cancer **4**:98-109 (Jan.) 1951.[17b]

16. Rouvière, H.: Anatomy of the Human Lymphatic System, Ann Arbor, Mich., Edwards Brothers, Inc., 1938.

17. (*a*) Semken, G. H.: Surgery of the Neck, in Nelson New Loose-Leaf Surgery, edited by A. O. Whipple, New York, Thos. Nelson & Sons, 1927, Vol. 2, pp. 763-905. (*b*) Ward, G. E., and Robben, J. O.: A Composite Operation for Radical Neck Dissection and Removal of Cancer of the Mouth, Cancer **4**:98-109 (Jan.) 1951.

18. Cited by Morfit, Surgery **31**:216-225 (Feb.) 1952.

19. Footnote deleted.

20. Footnote deleted.

21. Sugarbaker, E. D., and Wiley, H. M.: Intracranial-Pressure Studies Incident to Resection of the Internal Jugular Veins, Cancer **4**:242-250 (March) 1951.

jugular vein is caused by accumulation of venous blood in the cranial cavity. Martin and his associates [1c] considered that this transitory increase in the pressure of cerebrospinal fluid is not the result of ligation of the internal jugular veins but may be the result of stimulation of the cervical sympathetic nerves, since such increases may be observed when the head is turned from one side to the other or even after unilateral ligation of the internal jugular vein. Martin and his group [1c] have reported 66 cases in which bilateral radical dissection of the neck was done without a fatality; they, like most authors, are of the opinion that no particular contraindication exists to the performance of this operation when bilateral cervical metastatic lesions are present or when recurrent lesions develop on the contralateral side after initial radical dissection of the neck. Martin and associates [1c] and, more recently, other authors [22] have performed one-stage, bilateral, radical dissection of the neck with no untoward effects except transitory facial congestion. However, we, as well as others,[23] are still of the opinion that bilateral dissection should be done in stages when this does not violate the fundamental principles of operative treatment for malignant disease. At least one worker [24] expressed the opinion that bilateral radical dissection of the neck in stages should be performed when the tongue is the site of the primary tumor.

PRESENT STUDY

Although it was not until recently (1951) that we accepted the principle of combined radical dissection of the neck and resection of the primary lesion in the treatment of oral and cervical malignant lesions, we have become increasingly enthusiastic about the possibilities of this approach to the problem.

We have reviewed the experience at the Mayo Clinic between March, 1951, and August, 1952, during which period 48 patients who had intraoral, labial, or laryngeal malignant lesions were treated by combined operations. One of these patients underwent a second operation on the neck and jaw because of a contralateral recurrence; thus, 49 operations were done, but this second procedure is not included in the tables. Three bilateral radical dissections of the neck are included in this group.

The location of the primary lesion in these 48 patients was as follows: lip 13, tongue 9, buccal mucosa 7, floor of mouth 6, and larynx 13. The average age of the patients at the time of operation was 56.5 years, with a range from 37 to 78 years. Four patients (8.3%) were 40 years of age or less, while 18 patients (37.5%) were 60 years of age or more. The series included 43 men and 5 women; no women were included in the group who had labial or laryngeal carcinoma.

Of the 48 lesions, 4 were adenocarcinomas of the cylindroma type; 1 of these 4 was primary in the tongue, 2 were in the floor of the mouth, and 1 was primary

22. (*a*) Morfit, H. M.: Simultaneous Bilateral Radical Neck Dissection: Total Ablation of Both Internal and External Jugular Venous Systems at One Sitting, Surgery **31**:216-225 (Feb.) 1952. (*b*) Perzik, S. L.: Simultaneous Bilateral Radical Neck Dissection with Recovery: Report of 2 Cases, Surgery **31**:297-306 (Feb.) 1952.

23. Beahrs, O. H., and Jordan, G. L., Jr.: Bilateral Radical Cervical Dissection for Malignant Lesions of the Head and Neck, Proc. Staff Meet., Mayo Clin. **27**:449-454 (Nov. 5) 1952. Footnote 22.

24. Meyer, H. W., cited by Ward and Robben.[17b]

in the submaxillary gland. The remaining 44 lesions were squamous-cell epitheliomas; 2 of these were undifferentiated Grade 4 lesions, whereas the malignancy of the remainder was Grade 2 or 3.

Previous definitive treatment, exclusive of biopsy alone, had been given before the patient registered at the clinic to 20 (57%) of the 35 patients who had intraoral malignant lesions, whereas only 1 of the 13 patients who had carcinoma of the larynx had been subjected to definitive therapy elsewhere. All but two of the patients who had labial lesions had been subjected to previous definitive treatment; in these patients, it was considered that the lesion had been controlled, only to have metastatic tumors develop in 4 months to 13 years. Irradiation was the method of treatment that had been used most frequently elsewhere.

Only 7 of the 35 patients who had intraoral carcinoma and none of the 13 patients who had laryngeal carcinoma had received definitive treatment of mandibular and cervical metastatic lesions. The duration of symptoms of the patients who had uncontrolled primary tumors ranged from 1 month to 15 years; the latter period occurred in a case of submaxillary cylindroma.

TABLE 1.—*Incidence of Metastasis to Cervical Lymph Nodes from Intraoral or Laryngeal Carcinoma, with Comparative Efficacy of Clinical and Histologic Detection*

	Lymph Nodes Involved							
	Submaxillary		Upper Deep Jugular		Middle Deep Jugular		Lower Deep Jugular	
Primary Lesion	Clin.	Hist.	Clin.	Hist.	Clin.	Hist.	Clin.	Hist.
Lip	14	12	0	4	0	1	0	0
Tongue	6	6	2	5	0	2	0	0
Buccal mucosa	7	7	1	4	0	1	0	1
Floor of mouth and submaxillary region	6	5	0	2	0	0	0	0
Larynx	3	0	10	8	7	12	1	5

Mandibular Involvement.—Tumors attached to or actually invading the mandible occurred in 20 of the 35 patients who had intraoral carcinoma. In 1 patient contralateral metastatic lesions attached themselves to the mandible after a previous resection of the neck and jaw, necessitating the same operation on the side of the recurrence; thus, mandibular involvement occurred 21 times in 20 patients. Actual osteolytic invasion of the mandible, as seen roentgenologically, occurred in only five of these. Hemimandibulectomy was part of the dissection in 29 procedures. In addition to those cases in which intimate attachment of the lesion to or invasion of the mandible was present, hemimandibulectomy was performed eight times to facilitate exposure of the posterior part of the tongue and the floor of the mouth. In two cases, the mandible was transected and retracted to permit better exposure for the intraoral and pharyngeal operation, after which the mandible was brought back to its normal position and fixed with wire.

Metastasis to Cervical Lymph Nodes.—The incidence of clinical diagnosis of metastasis to the cervical lymph nodes and the actual findings on histologic study of the surgical specimen are compared in Table 1. In cases of intraoral carcinoma, clinical determination of metastasis to the cervical nodes is most accurate when large masses that obviously are cancerous are noted in the submaxillary, sub-

mandibular, and mandibular regions. Poor correlation was noted between clinical and histologic diagnosis of metastasis in the deep jugular chain of nodes in cases of intraoral carcinoma, since carcinoma was found histologically in the deep cervical nodes about seven times as often as expected from clinical examination.

In carcinoma of the larynx, metastatic lesions first occurred in the upper and middle jugular nodes; they frequently attained such a size in these locations that accuracy of clinical examination was greatest in these groups of nodes and diminished as lymph nodes at greater distances were involved. No histologic evidence of metastasis to cervical nodes was found in seven cases of intraoral carcinoma and in two cases of laryngeal carcinoma.

Distant metastatic lesions probably were present in one patient at the time of operation. This patient presented a large mass attached to the mandible; the mass was secondary to a primary submaxillary cylindroma. Roentgenologic shadows suggested the presence of pulmonary metastatic lesions. A combined but modified dissection of the neck and hemimandibulectomy were performed in order to relieve intractable severe pain in the jaw.

TABLE 2.—*Incidence of Symptoms in Intraoral or Laryngeal Carcinoma*

	Symptoms						
Primary Lesion	Tumor Only	Dysphonia	Pain	Mandibular Immobility	Loss of Weight	Bleeding	None
Lip	4	..	4	6	3	1	..
Tongue	1	..	7	1	4	..	1
Buccal mucosa	2	..	4	4	1	..	..
Floor of mouth and submaxillary region	2	..	4	2	1	..	..
Larynx	1	11	8	..	6	5	..

Symptoms.—Table 2 shows the frequency of various symptoms presented by the patients included in this study. Pain and immobility of the involved parts constituted the most frequent complaint in patients who had intraoral carcinoma, whereas dysphonia with or without pain in the throat was the commonest symptom in patients who had laryngeal carcinoma.

About a fourth of the patients who had intraoral carcinoma had no symptoms except awareness of a tumor, either in the mouth or in the neck. One patient who had carcinoma of the larynx presented no symptoms referable to the primary lesion but sought medical attention because of the development of a cervical tumor.

Operative Procedures.—The wide variety of combined procedures carried out in this series of patients is shown in Tables 3 and 4 and in Figures 1, 2, and 3. It will be observed that in two cases unilateral suprahyoid dissection of the upper part of the neck was combined with removal of the primary lesion; radical dissection was not performed because of the general condition of one of these patients and the presence of pulmonary metastatic lesions in the other. They are included in the series because en bloc excisions were carried out even though the dissections were limited inferiorly. For the same reason, two cases in which the internal jugular vein was preserved on one side are included, although the cervical portion of the operation must be considered as a limited dissection.

Ligation of the external carotid artery was carried out in 23 of the 36 combined procedures for intraoral tumors in order to minimize hemorrhage during the intraoral phase of the operation and during the postoperative period. Temporary tracheostomy was performed during 30 of the combined operations for intraoral malignancy.

Mortality.—Three deaths occurred among the 48 patients who had 49 operations for intraoral or laryngeal carcinoma; thus, the mortality rate associated with these 49 operations was 6.1%. The cause of two deaths was thought to be myocardial infarction; the third death was considered to be caused by pneumonia. Previously

TABLE 3.—*Incidence of Various Operative Procedures in Treatment of Intraoral Carcinoma*

Type of Operative Procedure	Location of Primary Lesion, Cases				
	Lip	Tongue	Buccal Mucosa	Floor of Mouth and Submaxillary Region	Total
Unilateral radical dissection of neck, hemimandibulectomy, removal of primary tumor	0	3	4	2	9
Unilateral radical dissection of neck, hemimandibulectomy, primary tumor removed elsewhere	10	1	3	..	14
Unilateral radical dissection of neck, removal of primary tumor	1	4	..	..	5
Unilateral radical neck and opposite suprahyoid dissection, removal of primary tumor	1	..	..	..	1
Unilateral radical neck and opposite suprahyoid dissection, hemimandibulectomy, removal of primary tumor	..	..	..	2	2
Unilateral suprahyoid dissection only, hemimandibulectomy, removal of primary tumor *	..	..	..	2	2
Bilateral, staged, modified dissection of neck; removal of primary tumor	..	1	..	..	1
Bilateral, staged, radical dissection of neck; bilateral mandibulectomy; primary tumor removed elsewhere	1	..	..	..	1

* One patient was in poor general condition; the other had pulmonary metastatic lesions.

TABLE 4.—*Incidence of Various Operative Procedures in Treatment of Laryngeal Carcinoma*

Type of Operative Procedure	Cases
Unilateral radical dissection of neck and laryngectomy	10
Bilateral, staged, modified dissection of neck and laryngectomy	1
Bilateral, staged, radical dissection of neck and laryngectomy	1
Bilateral, simultaneous, radical dissection of neck and laryngectomy	1

reported operative mortality rates ranged from 4 to 18%. No deaths occurred among the 13 patients in whom combined dissection of the neck and laryngectomy were carried out.

Morbidity.—The duration of hospitalization ranged from 6 to 90 days; the average was 21 days and the mean 14 days. Development of orocutaneous fistulas was the commonest cause of prolonged hospitalization. Such fistulas developed in eight patients; in seven of these, the fistulas closed spontaneously, whereas surgical closure was necessary in one.

During the postoperative period, a minimal degree of pyrexia occurred. The average highest temperature was 100.5 F. In five patients the temperature did not reach 100 F. Fever abated in an average period of 5.2 days.

Mild depressive psychosis developed in two patients and subsided without active therapy. In three patients, moderate disorientation and depression occurred that required active psychiatric treatment. All patients recovered completely.

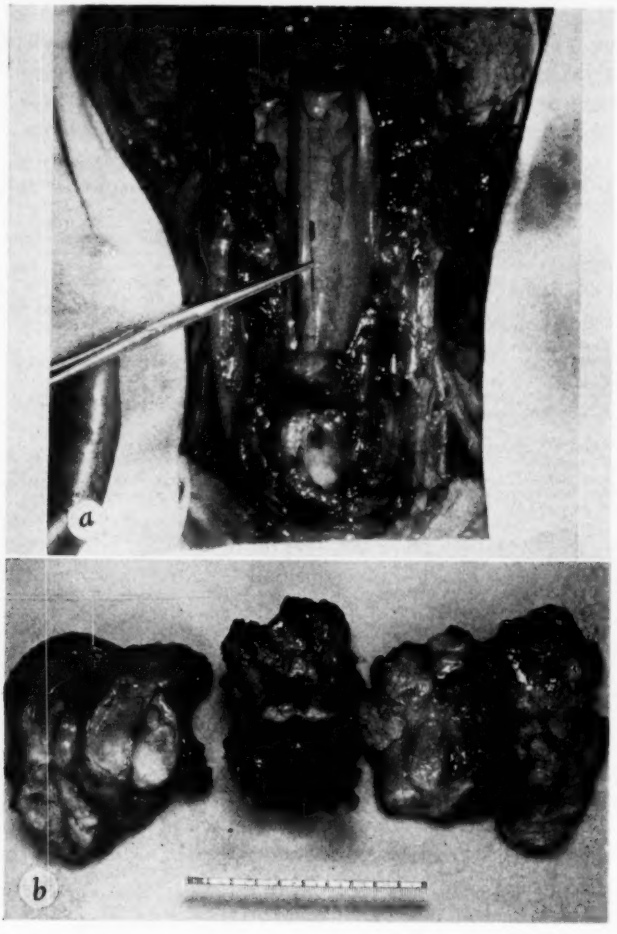

Fig. 1.—This patient had an extensive squamous-cell epithelioma of the extrinsic part of the larynx, with massive bilateral metastatic tumors. Bilateral radical dissection of the neck and total laryngectomy were done in one stage; *a*, at completion of the dissection; *b*, surgical specimen. The patient was well six months after operation.

One patient experienced prolonged dysphagia after almost total glossectomy but now has recovered the ability to swallow. Three patients complained of moderate pain in the contralateral temporomandibular joint resulting from shift of the mandible. In no instance did patients have to readjust to the deformities resulting from operative treatment.

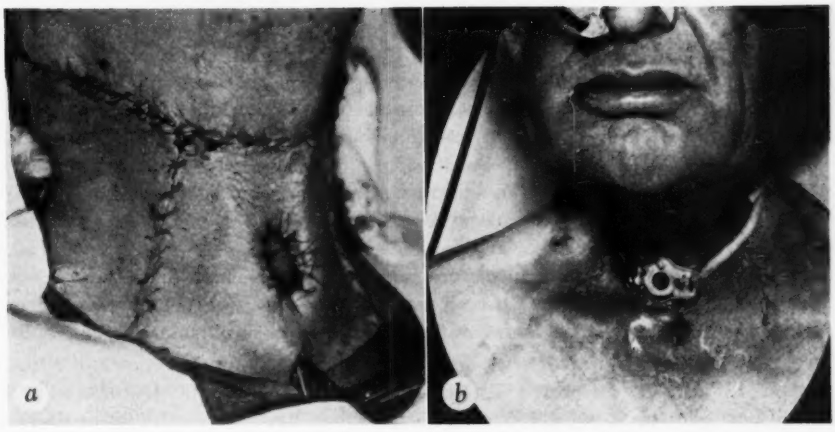

Fig. 2.—The patient represented in Figure 1: *a*, at completion of operation; *b*, one week after operation.

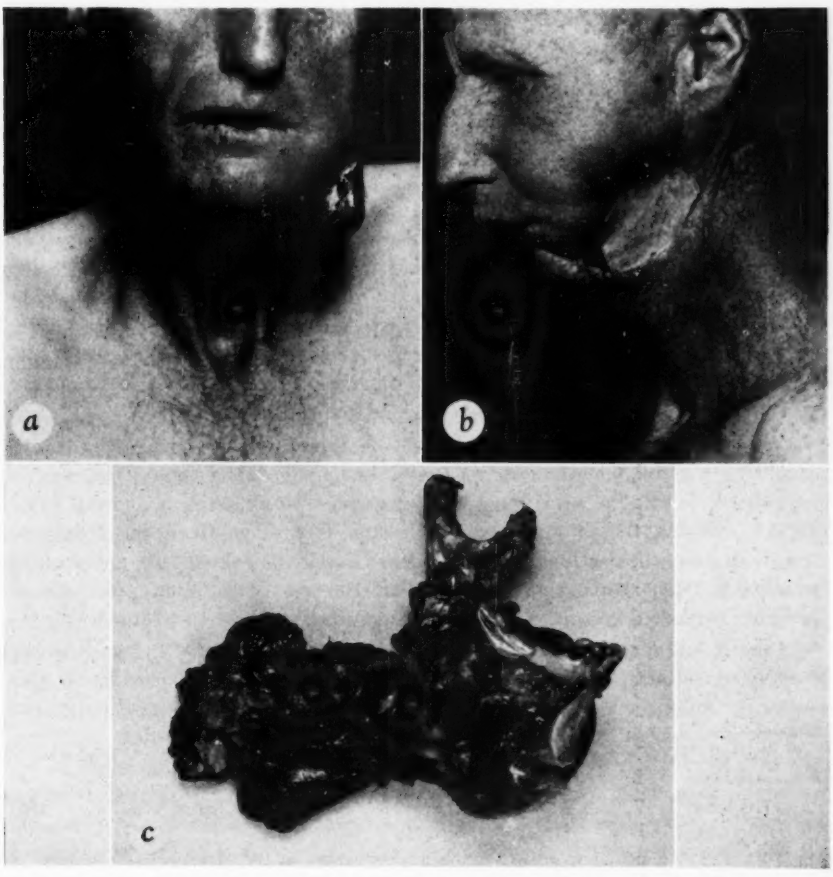

Fig. 3.—This patient had a metastatic mass of the left mandible and submaxillary region, secondary to primary squamous-cell epithelioma on the left lower lip treated previously by irradiation. Radical dissection of the left side of the neck, hemimandibulectomy, application of a skin graft to the defect, and temporary tracheostomy were done; *a*, before operation; *b*, three weeks after operation; *c*, surgical specimen.

Follow-up Studies.—Of the 46 patients who survived the initial combined operation for intraoral or laryngeal carcinoma (one of the three deaths occurred after the secondary operation already mentioned), 43 have been followed for periods ranging from 5 to 22 months. No evidence of recurrence of the carcinoma after the combined procedure and no significant postoperative problems secondary to the operation have been noted in 26 patients. During the follow-up period, four patients returned because of recurrences and subsequent definitive operations were carried out, with no evidence of subsequent recurrence. Inoperable recurrent lesions were found in six patients; only palliative treatment has been given in these instances. Death because of recurrent carcinoma has occurred in seven patients.

Although the rate of recurrence during the short follow-up period in this series is great, it must be remembered that the majority of these patients had lesions for which only incomplete or palliative treatment would have been carried out previously. It is also to be noted that these patients, for the most part, have lived in relative comfort for varying periods, while before they would have experienced severe pain, foul necrosing lesions, and starvation.

COMMENT

It is apparent from this study and from a perusal of other reports of series of combined operations for intraoral or laryngeal malignant lesions that the mortality and morbidity associated with these operations are comparable to those of other major surgical procedures for malignant disease and are not of such proportions as to relegate these operations to a place of last resort for patients who are hopelessly carcinomatous. The disabilities and disfigurements resulting from combined operations, especially when half of the mandible is removed, do not cause major mental or physical disruption of the future life of the patient. A combined dissection of the neck and hemimandibulectomy may be indicated frequently in the presence of incurable carcinoma to relieve the patient of severe pain. With evidence that many patients who have advanced stages of intraoral or laryngeal carcinoma can be salvaged by this surgical approach, it appears justified to extend it to the earlier stages of the disease, as has been done and reported by many.

In the light of our experience and that of Martin and associates,[1c] Morfit,[22a] Slaughter,[1d] Carroll,[25] and others, we are of the opinion that primary treatment in many cases of intraoral or laryngeal malignant disease must be considered to be surgical, utilizing the combined approach, and that other treatment should be carried out only when such an operation is inadvisable. We do not use preoperative radiation therapy, as recommended by Hendrick and Ward,[26] but proceed with operation without delay, as recommended recently by Vieta and Mulé.[27]

If the intraoral or laryngeal primary lesion is locally excisable and no evidence of cervical metastasis is present, then only the primary lesion need be treated surgically. Subsequently, if cervical metastatic lesions appear, radical dissection of

25. Carroll, W. W.: Application of Combined Hemimandibulectomy and Neck Dissection to Oral Carcinoma, A. M. A. Arch. Surg. **64**:647-654 (May) 1952.

26. Hendrick, J. W., and Ward, G. E.: Treatment of Intraoral Cancer, J. A. M. A. **150**: 1099-1103 (Nov. 15) 1952.

27. Vieta, J. O., and Mulé, J. E.: Combined Operations in the Management of Cancer in the Head and Neck, Am. J. Surg. n. s. **83**:734-745 (June) 1952.

the neck should be done. A primary combined procedure is indicated whenever metastatic lesions are detectable clinically in the cervical nodes. A hemimandibulectomy should be considered an essential part of the operation if such a procedure is necessary for exposure or if the primary lesion or metastatic tumors involve or encroach on the bone. If cervical metastatic lesions are not clinically evident but it is necessary to resect the mandible or otherwise open the neck, it is our opinion that a radical dissection of the neck should be done as part of the definitive operation. If this is not done and subsequent dissection of the neck becomes necessary, technical difficulties of the dissection are greatly increased by scarring. A modified suprahyoid dissection has little place in the treatment of intraoral lesions except in selected cases in which extreme risk to the patient or other unusual circumstances are present. Fewer and fewer indications exist for the so-called prophylactic dissection of the neck. An adequate follow-up is essential in the proper care of these patients; the danger of possible cervical metastasis and the necessity for close supervision must be impressed on them.

Dissection of the neck should always be as radical as possible, with removal of all nonessential cervical structures. The sternocleidomastoid, omohyoid, digastric, and stylohyoid muscles; the internal and external jugular veins; the spinal accessory nerve; the submaxillary salivary gland; the lower pole of the parotid gland, and the surrounding fascia, adipose tissue, and nodes should all be sacrified. This procedure leaves only the vertebral muscles, the carotid artery, and the phrenic, hypoglossal, sympathetic, and vagus nerves.

If subsequent clinically evident, contralateral, metastatic lesions appear in the nodes, a second complete radical dissection of the neck should be accomplished. Initially, if bilateral cervical metastatic lesions are present, a primary bilateral dissection of the neck can be carried out, but a staged procedure is considered to be preferable in most cases.

Few surgeons will argue about the unequivocal indications for composite operations, such as osteolytic involvement of the mandible and metastatic lesions of the cervical nodes regardless of whether the primary lesion is controlled or uncontrolled, persistent or recurrent postirradiation carcinoma involving perimandibular soft tissues with or without extension to the cervical nodes, or extensive carcinoma of the larynx with obvious metastasis to cervical nodes. Likewise, not many surgeons performing these operations will question today the necessity of hemimandibulectomy when the mandible is an anatomic barrier to access to the mouth and a deterrent to successful reconstruction, even though resection of the mandible, when it is not involved by malignant disease, does not appeal to those unacquainted with the technical aspects of these radical operations. It is rather at the other extreme that uncertainty and argument exist. Thus, not many surgeons today would advise combined or composite operations in every case of intraoral or laryngeal malignant disease, yet if the principles of adequate operative treatment for malignant disease were applied in their entirety, including wide excision of the primary lesion, the intervening lymphatic vessels, and the regional lymph nodes, such advice would be necessary. Utilization of such radical surgical procedures, tempered by judgment as to the degree of disability to be reasonably justified, is the only path left open for the surgeon who wishes to improve rates of cure in malignant disease of the head and neck.

SUMMARY

Forty-eight patients who had extensive intraoral or laryngeal carcinoma were treated at the Mayo Clinic by various surgical procedures utilizing a combination of excision of the primary lesion and radical dissection of the neck. The lesions in many of these patients would have been considered inoperable by previous criteria. A hospital mortality rate of 6.1% was associated with the 49 operations performed on these 48 patients. Of the 46 patients who survived the initial operation, 43 were followed for periods ranging from 5 to 22 months; 26 are well and have had no evidence of recurrence, 4 are well after subsequent operations for removal of recurrent lesions, and 13 have died because of carcinoma or are living but have inoperable recurrent lesions.

Combined dissection of the neck and resection of the primary lesion for intraoral or laryngeal carcinoma are advocated in all cases in which it is technically possible to excise completely the primary lesion and the cervical metastatic lesions or in which it is necessary to do a hemimandibulectomy or otherwise open the lateral portion of the neck. It is hoped that extension of these radical surgical procedures to patients in whom the disease is in early stages will increase sharply the long-term survival rates for patients who have intraoral or laryngeal malignant disease.

DISCUSSION

DR. WALTER W. CARROLL, Chicago: When Dr. Beahrs suggested that I comment on his paper, there immediately came to my mind many thoughts pertaining to the development of this type of work. Certainly, this presentation represents a tremendous amount of work, and he should be complimented upon it.

With no reference to any group in any part of this country or the world, I believe that if we study these problems we will come to the conclusion that in many localities good cancer therapy is limited by a tendency to retain current conservative methods and to avoid that procedure which seems to be difficult and deforming. When one tries to justify a therapeutic approach of this type, consideration of basic pathogenesis is essential. If I may have the first slide, I should like to bring to your attention the cervical lymphatics.

[Slide] We now know that lymphatic metastases occur by somewhat predictable routes of embolization. The process of embolus formation results in the collection of tumor cells in regional lymph nodes which frequently lend themselves to surgical excision.

When we review our experiences, we come to the realization that a primary carcinoma (for example, if it were in the tongue, or as diagramed on this slide) can be eradicated by excision or by irradiation, but that the same tumor will produce a distressing degree of radioactive resistance within the regional lymph nodes. From this we conclude that radical neck dissection, when used as a part of the original plan of treatment, is the more suitable method for eradicating regional metastases. Thus, there has developed the concept of the dissociated surgical approach in which the primary neoplasm is eliminated in one phase and the secondary neoplasms in another. This is a totally acceptable procedure and, when successful, produces a rather salutary salvage of intervening tissue.

In the presence of massive involvement or a recurrence in the primary site, the surgeon is confronted with the problem of spread by permeation, embolization and lymphatic blockade having been prior developments. The resultant retrograde spread is more unpredictable; consequently, in such circumstances, with the realization that irradiation is not the therapeutically complete answer, appropriate therapy must include the concept of excision in continuity.

[Slide] This slide demonstrates exactly what is meant by this. The gingival carcinomas have given us the lead for this evolution in surgical procedure. These lesions produce embolic metastases to the jugular subdigastric nodes in addition to contiguous proximal involvement of the submaxillary nodes. In such instances there is no choice but excision in continuity.

The next slide will show what the problem is if we have an irradiation failure when the primary neoplasm is located on the lateral aspect of the tongue or in the floor of the mouth. The perimandibular lymphatics become involved so that hemimandibulectomy in continuity with radical neck dissection is mandatory for clinical arrest.

[Slide] The logical expansion of this concept gives rise to the following question: "If such a procedure is of value, shall we exclude irradiation and rely entirely upon surgery?" This Kodachrome shows an example of a nonirradiated primary neoplasm in the floor of the mouth removed in continuity with homolateral neck dissection and the opposite submaxillary tissues. Now, is this too much to do, or not? I am not quite sure, but I present it for your consideration. Perhaps this primary neoplasm could have been controlled roentgenologically, and perhaps this dissection could have been done as a dissociated procedure with preservation of the mandible. Nevertheless, this is an example of the in-continuity procedure performed without previous irradiation. This man is comfortable and well four years after surgery.

[Slide] As we consider the patient with carcinoma of the larynx, we are confronted with serious emotional problems. Great extremes have been used to try to preserve the voice in the presence of laryngeal carcinoma. Arguments have been presented as to the minimum degree of local extension, as well as to lymphatic involvement, so that the cure rates are not as high as could be obtained by a more objective approach. Although the lymphatic drainage from the vocal cord area is small, that from the extrinsic larynx and the entire pharyngolaryngeal region is considerable; consequently, the latter lesions produce many direct metastases into the jugular chain. While laryngectomy has become an accepted procedure for some of these lesions, the problem of regional lymph node metastases has not been resolved. This next slide demonstrates a surgical specimen after combined radical neck dissection with laryngectomy when enlarged nodes were found in one jugular chain. This is a very feasible procedure and is being done now in more areas. An excellent advance, as demonstrated today by Dr. Beahrs, pertains to the use of bilateral dissection for those lesions in which the lateralization of metastases is difficult to ascertain or already has taken place. In time this might well become the accepted procedure for those lesions with a high percentage of regional lymph node involvement.

In the general field of head and neck cancer, excluding eye and brain, we are having experience which I am sure will eventually produce for us a more stable philosophy underlying the treatment of these lesions. We are not going to give up completely the dissociated procedures, and, on the other hand, we will undoubtedly add to our therapeutic armamentarium some applications of the in-continuity procedures that prove most efficient and appropriate. There has been a prejudice against the use of a major operation for a small lesion in this particular field, despite the general therapeutic trend toward a more vigorous approach against neoplasms in the deeper portions of the anatomy, as in the chest, abdomen, and pelvis. In time we will undoubtedly conclude that for the head and neck cancers there are real indications for major operations for small primary neoplasms.

LOCALIZATION OF RADIOACTIVITY IN REGIONAL LYMPH NODES

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PROBLEM

THE DIAGNOSIS of an inoperable carcinoma with regional metastases often leaves the surgeon with little to offer the patient.[1] Radiation therapy is resorted to, but this method has definite well-known limitations. In an effort to overcome the limitation of conventional radiation therapy, we attempted to utilize radioisotopes to localize radiation to the tumor and its regional metastases. This method utilizes the ionizing effect of the isotope as the source of radiation. A colloidal solution of radioactive element is injected into the tumor or organ involved. The colloidal particles are then apparently engulfed by phagocytes and carried through the lymphatics to the regional lymph nodes.[2] If the amount of radioactivity deposited in the tumor and the lymph nodes is sufficient to deliver effective radiation, a certain degree of palliation should be anticipated.

Two organs, the lung and the urinary bladder, were utilized in these experiments. The method can probably be applied to other organs in the body.

ISOTOPE

Radioactive colloidal gold (Au^{198}) was used. It was chosen primarily because its availability and short half-life (2.7 days) make it a convenient laboratory isotope. The strong beta rays (0.97 mev), which penetrate less than 1 mm., are the

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This work was done under the supervision of Dr. Marshall Brucer, Chairman of the Medical Division of Oak Ridge Institute of Nuclear Studies. Miss Germaine Click contributed technical help and advice.

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2. (*a*) Flocks, R. H.; Kerr, H. D.; Elkins, H. B., and Culp, D.: J. Urol. **68**:510 (Aug.) 1952. (*b*) Sherman, A. I.; Nolan, J. F., and Allen, W. M.: Am. J. Roentgenol. **64**:75 (July) 1950.

primary ionization source. The less energetic gamma rays (0.41 mev) are useful for external counting.[3] The isotope, obtained from Abbott Research Laboratory of Oak Ridge, Tenn., is a colloidal solution of particle sizes stated to range from 0.003 to 0.004 μ.

METHOD

Apparently healthy mongrel dogs were used. The dogs were anesthetized with sodium pentobarbital, administered intravenously, 30 mg. per kilogram of body weight.

Lungs.—Two methods were tried.

1. Instillation: Through a bronchoscope, a ureteral catheter was placed in a segmental bronchus. The bronchoscope was then removed, the head of the dog was elevated 12 in. (30 cm.), and the colloidal Au^{198} was injected into the catheter. The catheter was removed. The dog was kept in the same position for several hours to avoid reflux of the solution.

Doses ranging from 2 to 5 mc. of colloidal Au^{198} in 5 cc. of isotonic sodium chloride solution were used in the instillation method. Of the five dogs that were observed for long-term effects, two dogs received 3 mc. each, one dog 15 mc., one 25 mc., and one 35 mc., all in 5-cc. volumes.

2. Injection: Through a bronchoscope a long needle (type used for injecting esophageal varices) was placed into the mucosal wall of the right intermediate bronchus. Radiogold was injected into the needle; 2 mc. in 2-cc. volume was used. The site of injection was then reexamined to detect proper delivery.

Bladder.—Under sterile conditions 5 mc. of colloidal Au^{198} in 5 cc. of isotonic sodium chloride solution, to which 300 turbidity units of hyaluronidase had been added, was injected into the muscular layer at the fundus of the bladder. Hyaluronidase was added because it has been suggested that it would create a more uniform dispersion of the solution throughout the muscular wall [4] and would probably allow a more effective lymphatic pick-up.

AUTOPSY AND ASSAY

The dogs were killed at intervals ranging from 5 to 61 days after administration of the isotope. Specimens taken from various organs, including lymph nodes, were examined for radioactive uptake and histologic changes (Figs. 1 and 2).

The tissues that were studied for uptake were weighed, digested in nitric acid, and diluted to 10-cc. volume. The activity in this wet sample was measured with an end-window Geiger-Mueller tube. All figures are recorded as the counts per minute per gram of fresh tissue, corrected for decay from the time of animal injections.

RESULTS OF ASSAY

Lung.—1. Instillation Method (Tables 1 and 2): Twenty dogs were used in this experiment. The results of the assay for radioactivity showed an extremely high uptake in the segment of lung into which the solution had been instilled. High levels were also found in some of the hilar lymph nodes. The longer the survival time, the greater was the number of lymph nodes that were found to have radioactivity. The uptake in other organs, and particularly in the spleen and liver, was very low, indicating absence of activity in the blood stream.[5] The five long-term survival dogs were studied only for histologic changes.

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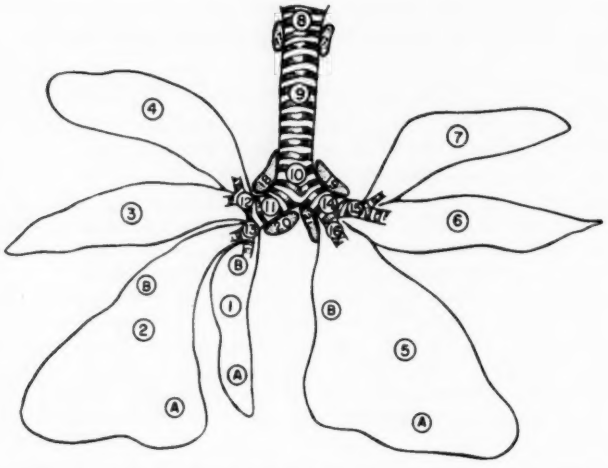

Fig. 1.—Schematic diagram of lung and regional lymph nodes of dog, indicating areas of assay.

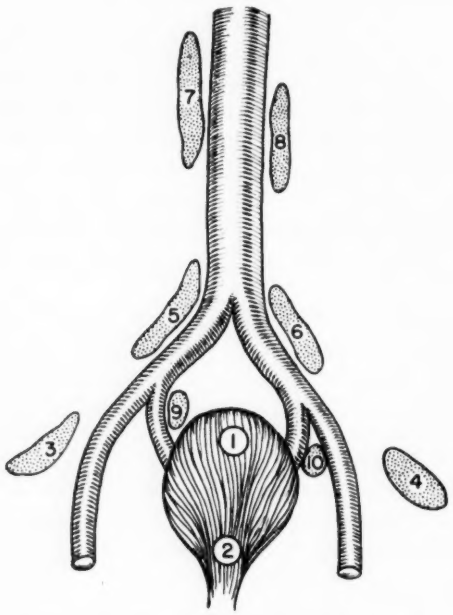

Fig. 2.—Schmeatic diagram of urinary bladder and regional lymph nodes of dog, indicating areas of assay.

TABLE 1.—*Radioassay of Nine Dogs After Instillation of Radiogold in Bronchus**

	Dog No.	73	74	75	82	71	72	80	76	77
	Amount of Au^{198} Mc.	3	3	3	3	5	5	3	3	3
	Time Interval, Days	5	5	5	5	6	6	6	7	7
No.	Anatomical Location									
1A	Cardiac lobe	0	14,600	140	8	0	0	0	15	10
1B		0	162,000	17,600	95	0	0	2	4	15
2A	R. lower lobe	25	220	710	170,000	2	15	6	10,300	977,000
2B		0	65	180	175	2,420	10,500	25	65	70
3	R. middle lobe	20,800	120	380	0	15	20	0	0	40
4	R. upper lobe	30	0	120	30	0	0	38,300	0	9
5A	L. lower lobe	5	40	10	45	0	0	250	0	15
5B		0	710	0	120	0	0	45	8	25
6	Lingula	0	25	9	110	15	0	0	20	30
7	L. upper lobe	0	40	9	25	4	0	30	70	35
8	U/3 trachea	—	—	—	—	—	—	—	—	—
9	M/3 trachea	0	0	0	60	8	20	35	15	45
10	L/3 trachea	—	—	—	—	—	—	—	—	—
11	R. main bronchus	0	160	650	45	0	0	0	10	180
12	R. upper lobe bronchus	—	—	—	—	—	—	—	—	—
13	R. intermediate bronchus	—	—	—	—	—	—	—	—	—
14	L. main bronchus	0	0	0	0	0	0	0	0	140
15	L. upper lobe bronchus	—	—	—	—	—	—	—	—	—
16	L. lower lobe bronchus	—	—	—	—	—	—	—	—	—
17	Upper tracheal L. N.	—	—	—	—	—	—	—	—	—
18	R. paratracheal L. N.	0	7	35	55	0	2,760	3	35	55
19	L. paratracheal L. N.	10	15	0	120	40	0	0	45	35
20	R. subcarinal L. N.	0	590	760	6,090	2,400	520	—	10	250
21	L. subcarinal L. N.	670	140	40	60	75	0	15	1,700	240
22	Heart	0	0	0	20	2	0	15	0	45
23	Liver	0	0	0	50	0	0	0	10	10
24	Spleen	0	8	0	65	0	0	0	0	180
25	Omentum	8	0	1	20	0	0	15	0	20
26	Kidney	0	0	1	30	20	4	0	0	30
	Background	16	16	16	16	17	17	16	18	16

* Colloidal Au^{198} instilled in right lower lobe bronchus through a catheter placed under direct vision with a bronchoscope. Figures are the count per minute per gram of tissue of organ, corrected for decay. Zero indicates count below background; a dash, no specimen.

TABLE 2.—*Radioassay of Eleven Dogs After Instillation of Radiogold in Bronchus**

	Dog No.	88	93	94	95	96	97	98	84	86	78	83
	Amount of Au^{198} Mc.	3	3	3	3	3	3	3	3	3	3	3
	Time Interval, Days	12	12	12	12	12	12	12	14	14	20	20
No.	Anatomical Location											
1A	Cardiac lobe	180	0	0	0	0	0	150	0	800	1,540	0
1B		260	0	0	570	1,450	170	970	140	65	120,000	65
2A	R. lower lobe	6,300	49,900	41,200	85,300	92,700	55,200	97,100	74,300	315	0	26,500
2B		0	5,390	0	480	0	0	300	65	20,700	1,520	330
3	R. middle lobe	200	0	0	25	170	20	35	150	340	250	210
4	R. upper lobe	0	0	0	190	25	0	35	210	280	0	0
5A	L. lower lobe	0	0	0	450	150	0	180	0	0	0	0
5B		25	65	15	120	0	90	85	0	0	1,470	0
6	Lingula	0	0	0	140	0	450	60	410	170	0	0
7	L. upper lobe	0	0	130	220	0	350	15	140	250	360	330
8	U/3 trachea	—	—	—	—	—	—	—	—	—	—	—
9	M/3 trachea	0	35	0	0	380	200	150	450	0	0	0
10	L/3 trachea	—	—	—	—	—	—	—	—	—	—	—
11	R. main bronchus	0	365	50	0	320	0	55	230	600	0	0
12	R. upper lobe bronchus	—	—	—	—	—	—	—	—	—	—	—
13	R. intermediate bronchus	—	—	—	—	—	—	—	—	—	—	—
14	L. main bronchus	115	0	0	960	60	200	0	0	0	0	0
15	L. upper lobe bronchus	—	—	—	—	—	—	—	—	—	—	—
16	L. lower lobe bronchus	—	—	—	—	—	—	—	—	—	—	—
17	Upper tracheal L. N.	—	—	—	—	—	—	—	—	—	—	—
18	R. paratracheal L. N.	0	310	370	300	320	0	230	270	22,800	3,850	41,500
19	L. paratracheal L. N.	60	120	760	0	130	200	0	2,300	0	1,060	500
20	R. subcarinal L. N.	610	1,370	0	11,100	4,520	5,000	2,850	720	4,400	940	32,600
21	L. subcarinal L. N.	260	60	65	120	210	14,000	15	70	180	6,780	14,600
22	Heart	0	150	0	65	0	4	60	0	0	770	0
23	Liver	0	0	150	0	0	0	450	0	100	0	0
24	Spleen	80	0	0	290	150	0	10	200	0	0	0
25	Omentum	0	0	6	0	10	135	0	180	0	0	0
26	Kidney	15	60	0	0	0	270	40	0	150	880	760
	Background	15	17	17	16	15	16	15	16	16	18	16

* Colloidal Au^{198} instilled in right lower lobe bronchus through a catheter placed under direct vision with a bronchoscope. Figures are the count per minute per gram of tissue of organ, corrected for decay. Zero indicates count below background; a dash, no specimen.

TABLE 3.—*Radioassay of Eight Dogs After Injection of Radiogold into Mucosa of Bronchus**

	Dog No.	105	115	111	116	118	119	120	117
	Amount of Au^{198} Mc.	2	2	2	2	2	2	2	2
	Time Interval, Days	5	5	5	5	5	5	5	5
No.	Anatomical Location								
1A	Cardiac lobe	150	30	130	0	30	15	55	60
1B		—	—	—	—	—	—	—	—
2A	R. lower lobe	920	0	25	15	54	0	7	10
2B		—	—	—	—	—	—	—	—
3	R. middle lobe	50	20	55	35	40	85	0	0
4	R. upper lobe	0	0	35	18,600	20	—	20	0
5A	L. lower lobe	10	0	9	35	15	30	4	30
5B		—	—	—	—	—	—	—	—
6	Lingula	20	0	20	250	20	25	9	20
7	L. upper lobe	0	0	15	20	20	50	6	0
8	U/3 trachea	55	60	0	65	30	8	35	0
9	M/3 trachea	7	0	80	0	5	50	120	120
10	L/3 trachea	100	35	175	400	5	770	60	680
11	R. main bronchus	—	—	—	—	—	—	—	—
12	R. upper lobe bronchus	120	190	1,900	0	35	9,500	160	0
13	R. intermediate bronchus	15	20,700	18,800	4,400	660	990	43,000	100
14	L. main bronchus	—	—	—	—	—	—	—	—
15	L. upper lobe bronchus	50	500	9,380	40	15	12,400	210	163,000
16	L. lower lobe bronchus	4,100	95,000	1,650	63	1,540	37,600	33,000	34,000
17	Upper tracheal L. N.	—	17,000	30,200	820	44,100	433,000	26,000	8,400
18	R. paratracheal L. N.	31,900	53,400	94,300	1,240	510	84,000	11,000	3,240
19	L. paratracheal L. N.	31,900	218,000	77,900	300	1,580	224,000	7,400	6,900
20	R. subcarinal L. N.	124,000	223,000	197,000	36,300	1,680	610,000	278,000	3,240
21	L. subcarinal L. N.	12,200	205,000	196,000	—	7,530	151,000	173,000	153,000
22	Heart	2	30	110	30	8	45	125	40
23	Liver	10	70	100	0	550	140	190	80
24	Spleen	9	15	20	—	220	60	130	80
25	Omentum	7	0	20	40	0	20	50	15
26	Kidney	3	9	15	0	4	2	20	0
	Background	16	16	16	16	16	16	16	16

* Colloidal Au^{198} injected into mucosa of right lower bronchus under direct vision with a bronchoscope. Figures are the count per minute per gram of tissue of organ, corrected for decay. Zero indicates below background; a dash, no specimen.

TABLE 4.—*Radioassay in Twelve Dogs After Injection of Radiogold into Wall of Urinary Bladder*

	Dog No.	110	109	113	114	81	87	92	99	100	103	104	108
	Amount of Au^{198} Mc.	5	5	5	5	5	5	5	5	5	5	5	5
	Time Interval, Days	5	5	5	5	13	13	13	13	13	13	13	15
No.	Anatomical Location												
1	Bladder, fundus	105,100	38,800	72,700	33,000	67,200	54,200	41,100	23,500	21,500	7,200	6,200	95,900
2	Bladder, trigone	59,900	10,600	53,300	370	31,000	760	9,270	4,250	80,600	48,700	41,700	4,290
3	R. inguinal L. N.	120	200	15	590	0	—	0	—	365	35	340	0
4	L. inguinal L. N.	65	75	140	740	0	60	0	9,340	235	65	80	0
5	R. iliac L. N.	5,950	51,600	61,800	8,400	164,000	3,460	10,900	13,190	26,200	22,600	1,210	146,400
6	L. iliac L. N.	22,000	860,800	21,600	19,800	79,800	131,000	6,320	56,000	94,600	19,800	12,300	2,930
7	R. aortic L. N.	520	—	371,000	56,200	0	100	31,000	—	—	780	740	58,400
8	L. aortic L. N.	1,730	1,800	33,400	0	850	440	19,000	1,290	550	440	1,570	—
9	R. hypogastric L. N.	127,300	269,000	—	720	0	—	—	—	—	92,100	370,600	154,100
10	L. hypogastric L. N.	121,000	119,000	620	15,600	0	—	—	1,160	—	—	—	10,400
11	Spleen	40	20	30	70	0	0	240	170	240	11,600	0	1,040
12	Lung	4	1	115	90	0	105	0	0	50	290	410	645
13	Heart	0	0	20	15	0	25	0	65	7	450	0	0
14	Liver	65	30	270	400	1,020	100	620	2,020	1,090	700	210	185
15	Kidney	110	40	0	0	30	60	130	60	65	0	245	175
16	Ureter	40	0	16,700	0	0	280	580	4,280	370	—	2,760	0
17	Mesenteric L. N.	—	60	—	110	85	5	340	280	75	240	0	100
18	Omentum	1,225	11,800	2,350	10,800	35,900	580	2,890	5,470	510	2,910	0	15,600
	Background	15	15	16	16	18	15	16	15	15	15	16	16

* There were injected 5 mc. Au^{198} and 300 turbidity units of hyaluronidase in 5-cc. volume into the fundic wall of the urinary bladder. Figures are the count per minute per gram of tissue of organ, corrected for decay. Zero indicates count below background; a dash, no specimen.

2. Injection Method (Table 3): Eight dogs were subjected to direct injection of the isotope into the mucosa of the right intermediate bronchus. In these the radioactive concentrations in all the hilar lymph nodes were consistently high. The uptake in the lung was minimal. In the one exception (Dog 116), there was undoubtedly some leakage at the time of injection. The levels in the liver, spleen, and other organs were extremely low. The site of injection showed a high level of activity but had a lower concentration than that found in the regional lymph nodes.

Bladder.—Twelve dogs were used. The radiation uptake counts in the various organs examined are given in Table 4. A high concentration was, of course, found at the site of injection in all dogs. A fairly consistent uptake with surprisingly high levels was found in the lymph nodes draining the urinary bladder. The nodes along the hypogastric artery, when these nodes were found, showed the highest

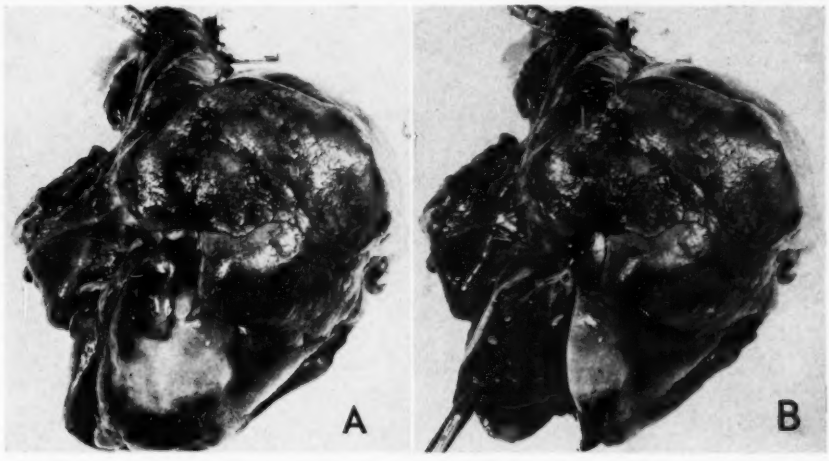

Fig. 3 (Dog 89).—*A*, large area of necrosis and pleural reaction in lower lobe of right lung (35 mc. Au^{198}). *B*, sectional surface of necrotic area.

activity. The iliac nodes and aortic nodes also showed relatively high concentrations. Very low counts were found in the liver and spleen, indicating that only a minimal amount of Au^{198} entered the blood stream.[5] A certain amount of spillage into the peritoneal cavity undoubtedly occurred during each injection. Free colloidal Au^{198} is rapidly picked up by the reticuloendothelial cells of the omentum, and this fact can explain the consistently elevated concentrations of radioactive material found in the omentum of all the dogs.[5]

The bladder trigone also had a consistently elevated level of radioactivity despite the fact that the injection site was several centimeters distant. This observation may be explained by the rich collateral lymphatic plexus of the urinary bladder as well as the dispersing activity of the added hyaluronidase.

PATHOLOGY

The lungs of seven dogs receiving 3 to 5 mc. of Au^{198} were examined 12 days after instillation of the isotope. The lower lobe segments of the right lung corresponding to the bronchus into which the Au^{198} was placed were all heavy, red, and noncrepitant. The remainder of the lungs

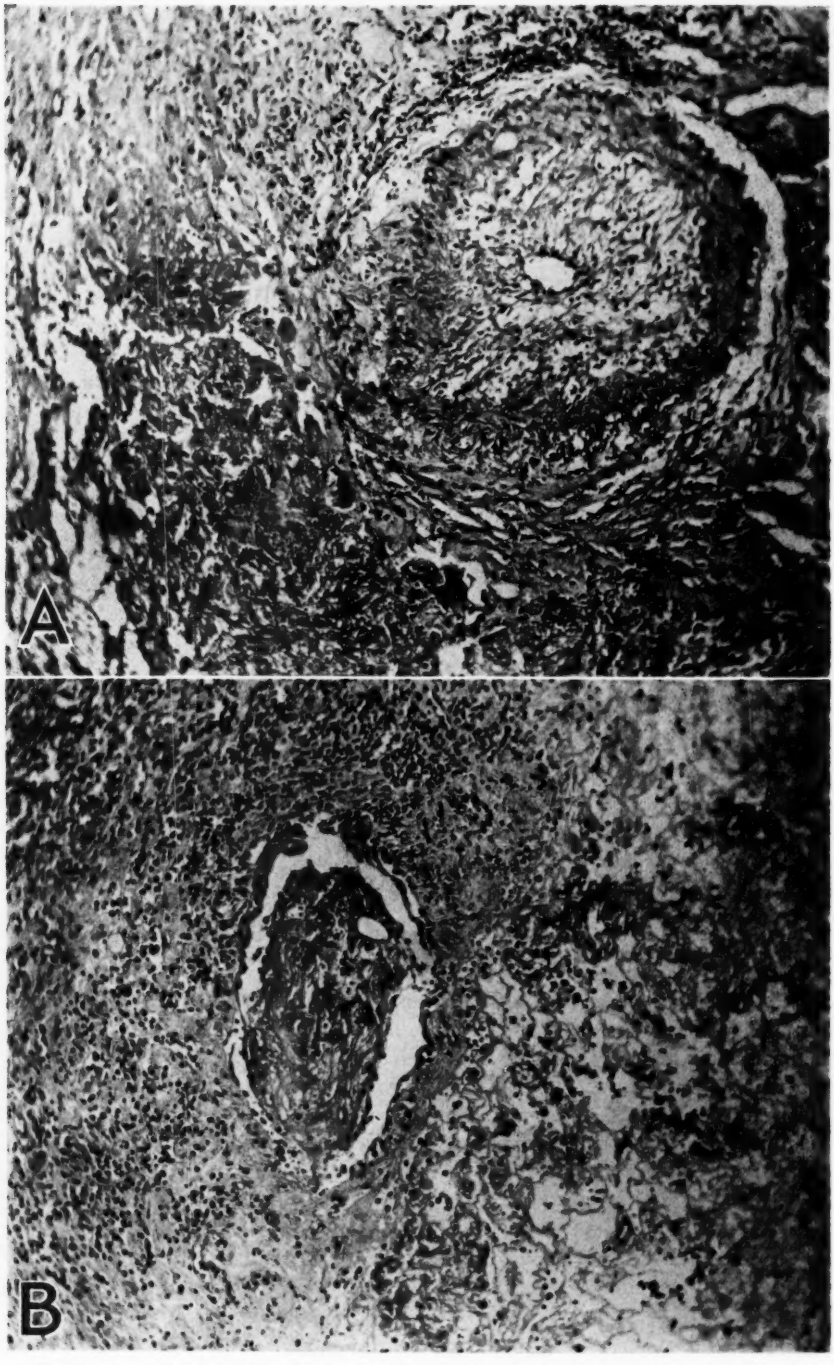

Fig. 4, *A* and *B* (Dog 90).—All parts of Figure 4 are photomicrographs of lungs instilled with radiogold. *A*, typical vascular changes and area of fresh necrosis of lung. *B*, characteristic changes in small bronchus. Regenerating epithelium is atypical. Black gold pigment can be seen in necrotic area.

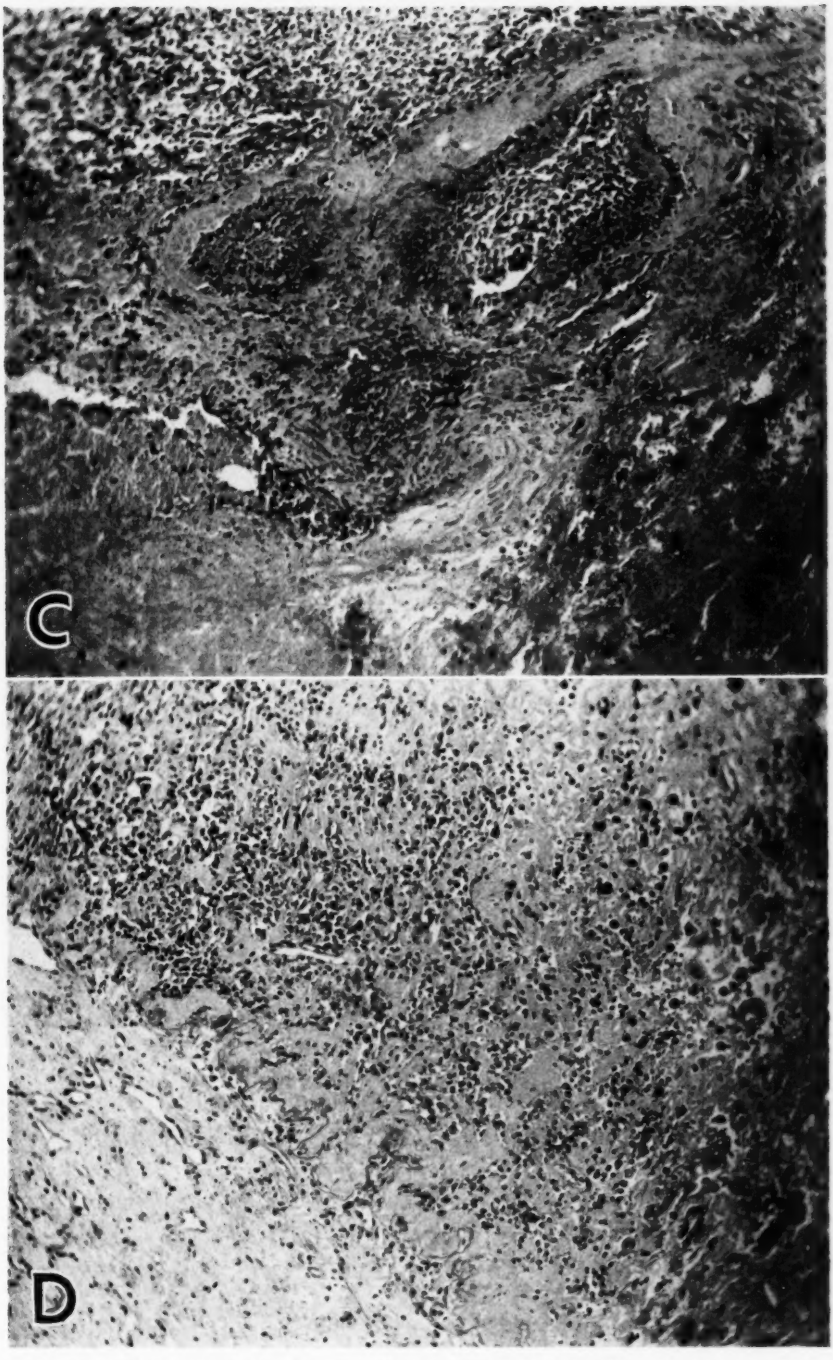

Fig. 4, *C* and *D* (Dog 91).—*C*, area of fresh necrosis and obliterative vascular changes. *D*, organizing area at periphery of lung. Fresh necrosis and black gold are seen on right. Thickened pleura is shown in lower left corner.

showed no significant changes, either grossly or microscopically. The involved segments were the site of edema, congestion, and atelectasis. The alveolar septa were thickened, and the lining cells were swollen; a few contained black pigment. There was extensive exudate in the alveolar sacs, composed largely of lymphocytes and monocytes. A single lung (Dog 95) showed fresh necrosis. Many of the bronchi contained loose granulation tissue and cellular debris. The epithelial cells of the larger bronchi appeared swollen, while the cells of the more terminal branches were pyknotic, with darkly staining nuclei and often very dense "fibrinoid" membranes. All sections showed heavy peribronchial cellular infiltrate. No significant vascular changes could be detected.

Two dogs were examined 14 days after instillation; one of these (Dog 86) showed fresh necrosis of the lung. Of two dogs killed after 20 days, one had marked segmental necrosis of the lung. In addition to the necrosis, all animals had pulmonary changes similar to the 12-day group.

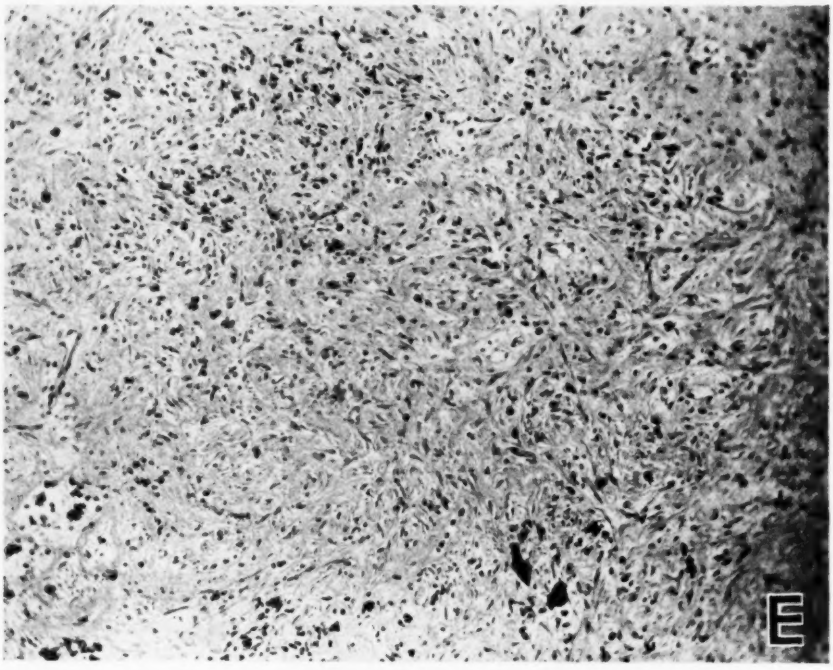

Fig. 4 *E* (Dog 89).—Irradiation scar.

One dog (Dog 89) was examined 61 days after the instillation of 35 mc. of Au^{198}. The posterior basal segment of the right lower lobe was firm, gray-white, and noncrepitant. The visceral pleura was gray, opaque and greatly thickened (Fig. 3). Multiple sections were examined from this area (Fig. 4), the surrounding lung, the left lung, and the regional lymph nodes. There was extensive necrosis of the grossly abnormal area, with only cell shadows remaining and with practically no leucocytic reaction. These areas contained numerous pigmented macrophages. In other areas there was fibroblastic proliferation and scarring or organization of the necrotic tissue. Many of the fibroblasts were large and of irregular shape. There was marked proliferation of new capillaries, with large endothelial cells throughout the areas of organization. The adjacent lung showed fibrous thickening of the walls of the air sacs and the various changes described in the previous series of low-activity animals. The larger bronchi to the involved segment showed no significant change; however, the more terminal branches all showed destruction of the epithelium with organizing granulation tissue in the lumen. There was

some regeneration of the epithelial cells, with numerous large atypical forms and poor cellular organization. The blood vessels showed marked changes in the nature of proliferative and obliterative endarteritis and endophlebitis with organizing thrombosis. Branches of all sizes were involved. The pleura was greatly thickened by well-organized, young fibrous tissue. The lymph nodes varied from 0.4 to 1 cm. Microscopically, they were of normal cellularity, with germinal follicles within normal limits. The only detectable changes were a slight increase in the

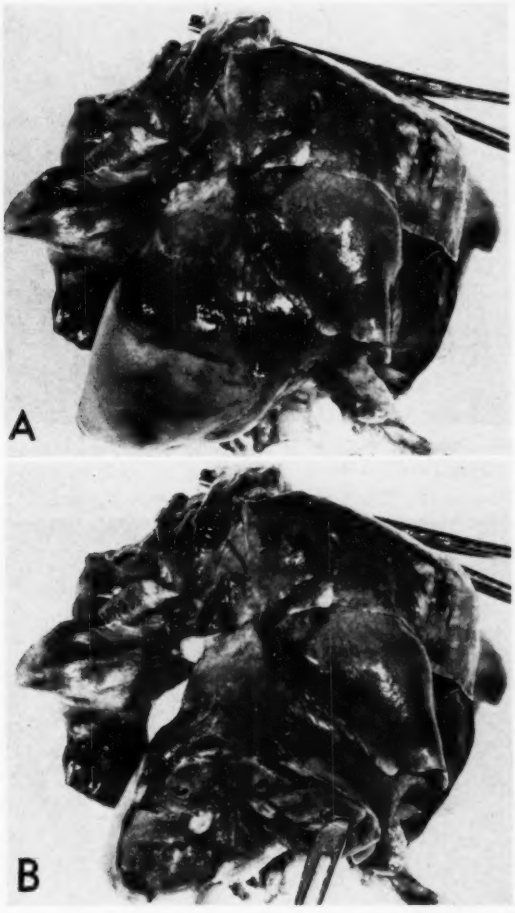

Fig. 5 (Dog 91).—*A*, large area of necrosis and pleural reaction in lower lobe of right lung (25 mc. Au^{198}). *B*, sectional surface of necrotic area.

number of plasma cells, moderate scarring, and focal conglomerations of reticulum cells. These changes were considered to be of a nonspecific nature. The liver was entirely within normal limits.

Dog 90, receiving 15 mc. Au^{198}, and, Dog 91 (Fig. 5), receiving 25 mc., were both examined after 61 days. The gross and microscopic findings in these two dogs were similar in all respects to those described for the high-dosage animal.

Bladder.—The urinary bladders of four dogs examined five days after injection all showed considerable thickening of the bladder walls for several centimeters around the site of injection;

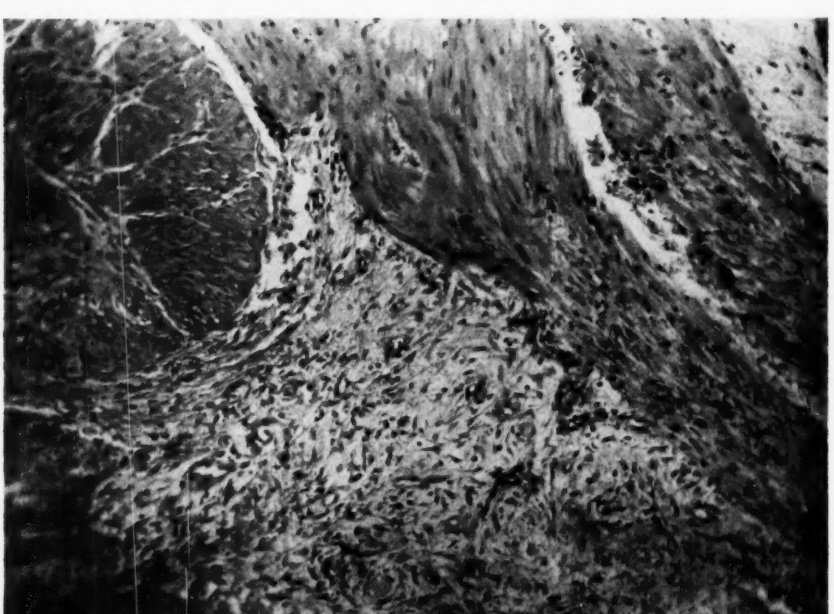

Fig. 6 (Dog 100).—Photomicrograph of section of urinary bladder injected with Au^{198}, showing necrosis of muscle and fibroblastic proliferation.

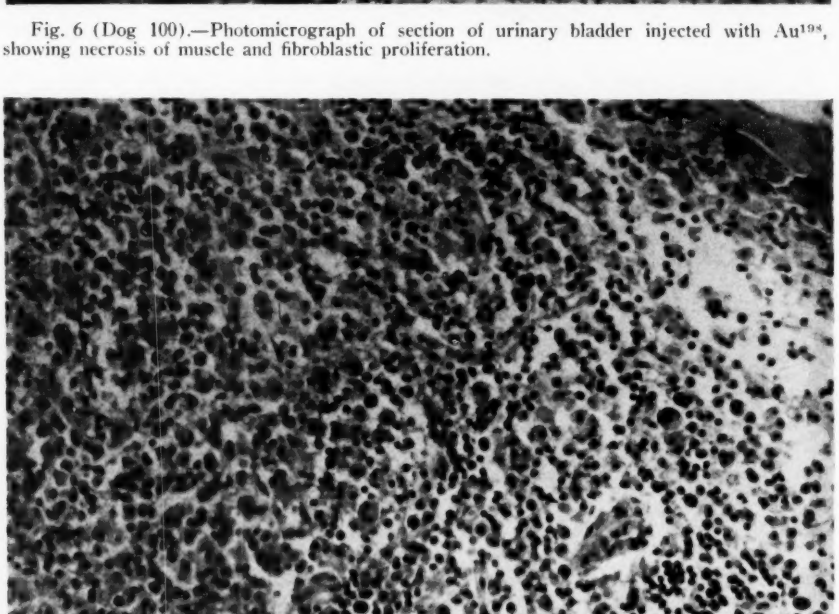

Fig. 7 (Dog 100).—Photomicrograph of a regional lymph node showing depletion and pyknosis of lymphocytes, increase in reticulum cells, and obliteration of peripheral sinus (right upper corner).

this was accounted for by edema and congestion. The areas near the injection site showed early necrosis of the muscle, with adjacent fibroblastic proliferation in a loose stroma rich in dilated capillaries (Fig. 6). The endothelial cells were swollen. There was a thin layer of fibrin on the peritoneal surface, with stratification of swollen mesothelial cells. With the exception of swelling of the transitional cells, the mucosa was not remarkable.

Seven dogs examined 13 days and one dog examined 15 days after injection showed changes in the urinary bladder similar to those in the first group with the exception that there was less fibrin on the peritoneal surface and rather marked fibroblastic proliferation beneath the peritoneum and in the muscle about the injection site. There was minimal mixed leucocytic response.

The regional lymph nodes in the last-mentioned group were small and could not be found in all cases. The histologic findings were qualitatively similar but differed somewhat quantitatively. The peripheral sinus was often packed with large pigment-containing mononuclear cells. In scattered foci the sinus was replaced by fibrous tissue rich in these pigmented cells. Only an occasional node showed marked fragmentation of lymphocytes. Plasma cells often made up from about one-sixth to one-fourth of the cellular element. Follicles with germinal centers were always present, but were apparently decreased in number, often showing only one or two in a cross-section (Fig. 7). No consistent change in blood vessels was noted.

The bone marrow was of normal cellularity without detectable maturation abnormalities.

COMMENT

Several reports on the use of isotopes in effecting localization of radiation in the lungs have been presented in recent years. Zn^{63} and Au^{198} have been introduced through a heart catheter directly into the pulmonary artery or its branches, and localization of radioactivity in the segment of lung supplied by the vessel has been reported.[6] Colloidal Au^{198} has been placed in the trachea of dogs lying on one side. This procedure resulted in high levels of activity in the lung on the dependent side and eventual concentration in the mediastinum.[7] Radiogold has been placed in the pleural cavity with resultant high levels of activity on the pleural surfaces of the lung and minimal activity in other organs.[5]

In these experiments we produced maximum localization of activity in the lung by the instillation method. A skilled bronchoscopist should be capable of localizing the segment to which the isotope is delivered. In the event of bronchus obstructed with carcinoma, it is conceivable that the instillation of an istope may produce sufficient radiation to shrink the tumor and open the bronchus. The injection method produced extreme localization in the hilar lymph nodes. It is of great interest that the levels in the nodes were even higher than those at the site of injection. A combination of the two methods may be the means of delivering sufficient radiation to afford a degree of palliation to the patient with far-advanced carcinoma of the lung.

The delivery of effective radiation to an inoperable urinary bladder cancer and the regional nodes by conventional radiation therapy has well-known limitations, particularly its damaging effect on adjacent structures. The method used in this experiment seems to accomplish a well-localized effect on the urinary bladder of dogs. At the same time, appreciable radiation is delivered to the regional lymph nodes, and a minimal amount of activity is detectable elsewhere in the body. If a higher-level dosage of activity were used, one might expect more necrosis at the injection site and higher concentration of activity in the lymph nodes.

6. Müller, J. H., and Rossier, P. H.: Acta radiol. **35**:449 (May-June) 1951.

7. Meneely, G. R.; Kory, R. C.; Auerbach, S. H., and Hahn, P. F.: Fed. Proc. **10**:365 (March) 1951.

Direct injection of colloidal Au^{198} into tumors has been done with reported success.[8] The major defect in this method has been the uneven dispersion of the radioactive particles, with failure to deliver uniform radiation. Results will undoubtedly be improved with the developments of better techniques.

It is important to remember that the dogs were healthy dogs without carcinoma. In the event that the lymphatics are "plugged" with metastatic emboli, it is possible that localization in the lymph nodes would not be as concentrated or would not occur. The only way we know to prove localization in this situation would be by clinical application and trial.

SUMMARY AND CONCLUSIONS

A colloidal solution of Au^{198} was instilled through a catheter into a selected segment of a lung in 20 dogs.

Assay of these dogs, killed at various time intervals, revealed localization of activity within the selected segment of lung and regional lymph nodes. Histologic studies showed radionecrosis produced in proportion to the amount of isotope instilled in the segment of lung. Only minor changes were seen in the lymph nodes.

A colloidal solution of Au^{198} was injected into the mucosa of the right intermediate bronchus of eight dogs. Assay revealed extremely high levels of concentration of radioactivity in the regional lymph nodes, a lower level at the sight of injection, and negligible activity elsewhere.

A colloidal solution of Au^{198} was injected intramurally into the urinary bladder of 12 dogs. Assay and histologic studies were made on dogs killed at various time intervals ranging from 5 to 15 days. Concentrations of radioactivity were found to be consistently high at the site of injection as well as in the trigone of the urinary bladder and in the regional lymph nodes.

Radiogold produced necrosis of the urinary bladder wall at the site of injection. Minor changes were noted in the regional lymph nodes.

These results suggest the possibility of a clinical trial in patients with inoperable bronchogenic and bladder carcinoma. Palliation might be afforded such patients by the use of these methods.

DISCUSSION

DR. JAMES CARPENDER, Chicago: It is always a pleasure to discuss a paper in which adequately documented experimental work, such as this, is presented, particularly when the authors themselves are careful to point out the possible weaknesses of the methods.

Their results with radioactive gold injected into the bronchial wall are suggestive of more than a hope of palliation. If the gold can be transmitted to the hilar nodes in effective amounts, perhaps such injections could be followed by radical surgery, with hope of cure in moderately advanced disease.

The instillation of gold gives me some cause for worry when I think of the danger of contamination of the surroundings, should the patient cough. I am sure our physicists would cast a rather jaundiced eye on this procedure, particularly since in our own institution we not only have to worry about contamination of personnel and surroundings, but we have to worry about difficulties imposed on other experimenters using low-level activities, should such contamination get out of the local area where is occurred.

8. Hahn, P. F., and Sheppard, C. W.: Ann. Int. Med. **28**:598 (March) 1948. Flocks and others.[2a] Sherman and others.[2b]

In the case of the bladder injections, I would be worried by the local necrosis at the site of injection, particularly since larger amounts of gold would probably have to be used for effectiveness in a malignant condition. Here, as well as in the lung, there is little histological change in the lymph nodes, indicative of the need for a higher dose.

The authors emphasize that these were normal dogs, and that when a tumor is present, the lymphatics may be blocked. They point out the need for clinical study, and I think they should be urged to undertake such study on the basis of their present results.

Dr. William D. Holden, Cleveland: These studies are beautifully done and well controlled. Dr. Berg did not have the opportunity or the time to go into the metabolism of radioactive gold at all, and I should just like to mention a few things that I think are of importance in considering the radiation that gold emits.

[Slide] If gold is injected intravenously, it behaves in a very characteristic manner. This represents radioactive iodinated albumin (the red line), and you can see the disappearance rate from the blood stream is extremely slow.

The blue line is radioactive Na^{24} and you can see that it disappears moderately rapidly, reaching equilibrium with the sodium contained in extracellular spaces.

On the yellow line, which runs almost parallel to the ordinate, you can see that the gold disappears very rapidly. The gold is taken up avidly by the reticuloendothelial system.

Gold injected into any particular organ is going to move by way of the lymphatic channels to the regional lymph nodes. That was very amply demonstrated by Dr. Berg. As you also saw, it is stopped at the lymph nodes. Very little of the radioactivity could be recovered in other organs, signifying that the gold was not transmitted through the thoracic duct into the venous circulation and then to other organs.

One of the things that would concern me about the practicable application of gold as an irradiation agent for regional metastases within lymph nodes is the fact that not only may the lymphatics be plugged but also many lymph nodes may be completely replaced by neoplastic tissue. I do feel, however, that further experimental and clinical work must be attempted. It will be difficult to evaluate results. Nevertheless, it is an excellent study and should be carried out as Dr. Berg plans.

Dr. Harold F. Berg, Louisville: I should like to answer something brought up by Dr. Carpender.

He mentioned the fact that we actually demonstrated very little change in the lymph nodes. That is true of the animals presented in the series in this paper. Subsequently, though, we had another series with slightly larger doses, and we definitely have found radioactive necrotic changes in the lymph nodes.

RELATIONSHIP OF PULMONARY FUNCTIONAL AND PATHOLOGICAL CHANGES IN MITRAL STENOSIS

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OCCLUSIVE vascular changes in the lung accompanying the pulmonary hypertension of mitral stenosis have been known to occur since their description by Brenner in 1935 [1] and by Parker and Weiss in 1936.[2] What part the pulmonary arteriolar and capillary changes may play in the distressing respiratory symptoms of mitral stenosis is a matter of concern. So, too, is their effect on the results of operations which restore relatively normal function to the stenotic valve. Larrabee, Parker, and Edwards [3] believed that patients with intimal or medial fibrosis of the arterioles would not benefit from the operation because of irreversible changes which would increase the resistance to blood flow through the lung. Our studies do not lead us to support this point of view. Physiological observations and study of biopsy specimens of lungs obtained from a series of patients who underwent mitral commissurotomy suggest that the ultimate clinical result of the operation is far less dependent upon the condition of the pulmonary vasculature than upon intrinsic factors, such as concomitant valvular disease or myocarditis, which affect the function of the heart.

The etiologic basis of pulmonary arteriolar sclerosis in patients with mitral stenosis has been conjectural. Since the demonstration by Welch and Kinney [4] that

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This work was done during the tenure by Dr. Hackel of a research fellowship of the American Heart Association.

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This investigation was supported in part by research grants H-1317 and H-852 from the Heart Institute of the National Institutes of Health, United States Public Health Service.

1. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**:211, 1935.

2. Parker, F., Jr., and Weiss, S.: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573, 1936.

3. Larrabee, W. F.; Parker, R. L., and Edwards, J. E.: Pathology of Intrapulmonary Arteries and Arterioles in Mitral Stenosis, Proc. Staff Meet., Mayo Clin. **24**:316, 1949.

4. Welch, K. J., and Kinney, T. D.: The Effect of Patent Ductus Arteriosus and of Interauricular and Interventricular Septal Defects on the Development of Pulmonary Vascular Lesions, Am. J. Path. **24**:729, 1948.

the changes accompany conditions in which there is a considerable increase in pulmonary blood flow, further studies [5] have shown that an increase in pulmonary vascular pressure plays its part. Muller, Dammann, and Head [6] have produced similar lesions experimentally in the dog by creating pulmonary hypertension with an aorta-pulmonary artery anastomosis. The present study indicates that, in addition to pressure, time is important in producing pulmonary arteriolar changes in man.

METHODS AND MATERIALS

The Patients.—Lung specimens were obtained at operation from 5 men and 11 women operated upon for mitral stenosis. The decision to operate was dependent primarily upon the presence of symptoms, such as dyspnea and limitation of activity, and upon signs of mitral stenosis and heart failure. This decision was aided by evidence of pulmonary hypertension found by cardiac catheterization. In no instance was a patient without symptoms operated upon because of a clinical diagnosis of mitral stenosis alone. As Table 1 shows, 1 patient was in Class II, 4 in Class IV, and the remainder (11) in Class III (classification of disability of the American Heart Association). Four patients were found at operation to have slight and three moderate mitral regurgitation. Slight aortic-valve regurgitation and stenosis were present in two patients. All patients were moderately or severely limited in their physical activities. Six had experienced hemoptysis. One or more attacks of acute pulmonary edema had occurred in all but one. Despite careful medical preparation, a slight degree of pulmonary edema was present clinically, as evidenced by basilar râles, in five at the time of operation. This was pronounced in two who were operated upon in frank failure as an emergency.

The operations performed were all essentially as described by Harken and associates [7] and Bailey, Glover, and O'Neill.[8] The index finger was inserted into the left auricle through its appendix, and an estimate was made of valvular incompetence if any by the systolic jet of blood against the fingertip. Commissurotomy was accomplished with the finger in 10 patients. A valvulotome was required for part of the procedure in six. In no patient was there an apparent postoperative increase in regurgitation. In four cases there was a remarkable decrease in regurgitation following complete release of the valve leaflets at the commissures. All operations were performed with the patient under endotracheal anesthesia, an ether-oxygen mixture being used.

Lung Biopsies.—Upon completion of the commissurotomy a small wedge biopsy specimen was obtained from the anterior portion of either the lingula or the lower

5. (*a*) Civin, W. H., and Edwards, J. E.: Pathology of the Pulmonary Vascular Tree: I. A Comparison of Intrapulmonary Arteries in Eisenmenger Complex and in Stenosis of Ostium Infundibuli Associated with Biventricular Origin of the Aorta, Circulation **2**:545, 1950. (*b*) Edwards, J. E., and Chamberlin, W. B., Jr.: Pathology of the Pulmonary Vascular Tree: III. The Structure of the Intrapulmonary Arteries in Cor Triloculare Biatriatum with Subaortic Stenosis, ibid. **3**:524, 1951. (*c*) Henry, E. W.: The Small Pulmonary Vessels in Mitral Stenosis, Brit. Heart J. **14**:406, 1952.

6. Muller, W. H., Jr.; Dammann, J. F., Jr., and Head, W. H., Jr.: Changes in the Pulmonary Vessels Produced by Experimental Pulmonary Hypertension, read before the Society of University Surgeons, St. Louis, 1953, Surgery, to be published.

7. Harken, D. E.; Dexter, L.; Ellis, L. E.; Farrand, R. E., and Dickson, J. F., III.: The Surgery of Mitral Stenosis: III Finger-Fracture Valvuloplasty, Ann. Surg. **134**:722, 1951.

8. Bailey, C. P.; Glover, R. P., and O'Neill, T. J. E.: The Surgery of Mitral Stenosis, J. Thoracic Surg. **19**:16, 1950.

TABLE 1.—*Data for Sixteen Patients Operated on for Mitral Stenosis**

Patient	Age	Sex	Class	Cardiac Catheterization at Rest: Preop. PA	Preop. PCP	Preop. CO	Postop. (6 Wk.) PA	Postop. (6 Wk.) PCP	Postop. (6 Wk.) CO	Preoperative Pulmonary Function: Vit. Cap. % N	Surg. Ind. WV MBC	Arterial O_2 Sat. Air	Arterial O_2 Sat. 15% O_2	Lung Pathology L/W	Lung Pathology CPH	Clinical Result	Comment
D. J.	31	F	III	26	21	3.7	20	15	3.9	89	0.16	94	88	1.55	..	Excellent	.....
J. L.	33	M	III	30	19	4.4	17	11	4.0	86	0.11	94	85	3.61	..	Excellent	.....
E. B.	27	F	II	26	21	4.5	18	15	3.7	95	0.13	92	90	4.23	0	Excellent	.....
M. D.	38	F	III	41	27	3.1	30	26	2.7	89	0.45	93	90	1.90	..	Good	Previous CVA; postoperative CVA
W. E.	28	M	IV	..	..	...	..	..	...	84	0.12	90	82	2.38	..	Good	.....
J. K.	47	M	III	46	38	3.8	21	15	3.1	75	0.18	91	84	1.85	..	Excellent	Moderate mitral regurgitation reduced postoperatively
L. E.	25	F	III	27	18	4.7	23	15	4.6	99	0.10	95	92	3.58	0	Good	.....
E. R.	37	F	IV	58	31	3.2	37	15	3.9	85	0.32	86	78	1.33	..	Excellent	Much improved 1 yr. postoperatively
R. W.	42	M	III	28	21	4.1	18	15	3.5	89	0.14	91	85	1.10	..	Fair	Moderate aortic regurgitation
L. S.	39	F	IV	33	28	3.2	..	..	...	84	0.19	90	84	2.94	..	Good	Previous CVA
I. S.	49	M	III	26	21	3.7	27	22	3.9	79	0.15	92	..	3.75	..	Fair to poor	Aortic regurgitation and tachycardia
E. Z.	43	F	III	39	26	3.9	..	..	...	86	0.21	93	91	3.44	0	Excellent	.....
S. G.	42	F	III	37	25	4.1	..	..	...	82	0.15	92	..	3.17	..	.....	No commissurotomy
L. H.	39	M	III	23	16	4.1	..	..	...	102	0.11	89	..	2.16	..	Good	.....
C. B.	32	F	III	37	23	3.8	19	10	5.1	89	....	95	..	2.47	..	Good	Mitral regurgitation reduced postoperatively
H. P.	46	F	IV	40	23	3.1	36	20	5.2	69	0.35	86	..	3.54	..	Excellent	Mitral regurgitation reduced postoperatively; asthma

* Abbreviations: PA, mean pulmonary arterial pressure; PCP, mean pulmonary capillary pressure; CO, cardiac output in liters per minute; Vit. Cap., vital capacity; Surg. Ind., surgical index; WV, walking ventilation (liters per minute); MBC, maximum breathing capacity (liters per minute); L/W, lumen-to-wall ratio; CPH, chronic passive hyperemia; CVA, cerebrovascular accident.

lobe of the left lung. Care was taken to avoid portions of the lung which had been rendered atelectatic during the operative procedure. The biopsy was cut with a scalpel and placed directly into 10% formalin. Paraffin sections were stained with hematoxylin and eosin, Masson's trichrome, and Weigert's elastic-tissue stain. The sections were studied microscopically with particular attention to the arterioles, the degree of septal fibrosis, and chronic passive hyperemia. Quantitative measurements were made of the walls and the lumina of arterioles ranging from 50 to 150 μ according to the method described by Kernohan, Anderson, and Keith.[9] To make these measurements the walls, exclusive of the adventitia, of vessels cut in cross section were measured at the four quadrants. The average of these values obtained was considered the wall thickness of a given vessel. Likewise, the lumen was measured by taking the average of two internal diameters at right angles to each other. In each section, at least 10 such vessels were measured. Those in proximity to bronchi were not measured, to escape confusion with bronchiolar arteries. The average value of lumina and walls was expressed as a ratio, lumen to wall, for each biopsy specimen. Specimens of lung from five persons without cardiac or pulmonary disease, chosen from the autopsy files of Cleveland City Hospital, served as controls. These persons were within the same age range as the patients with mitral stenosis, the mean age of the control group being 38, as compared to 36 in the mitral-stenosis series. The sections from these controls were stained and examined in the manner described.

Cardiac Catheterization.—Conventional right-heart catheterization was performed in all but one patient, in whom acute pulmonary edema developed during the procedure. The oxygen content of blood in the superior and inferior venae cavae, right atrium, ventricle, pulmonary artery, and brachial artery was determined spectrophotometrically [10] or by the manometric method of Van Slyke and Neill.[11] Pressures were obtained in all chambers, including so-called "pulmonary capillary pressure," and recorded on the Brush multichannel oscillograph via Statham strain gauge transduction. Total body oxygen consumption was determined simultaneously. Cardiac output was calculated by the Fick principle. When practicable, all determinations were repeated during the last two minutes of a four-minute leg-raising exercise period. Cardiac catheterization was repeated six weeks postoperatively in nine patients and again at the end of a year in four patients.

Measurements of Pulmonary Function.—The respiratory function of each patient was recorded preoperatively and six weeks postoperatively. Timed vital capacity was determined by the method of Gaensler, Rayl, and Donnelly.[12] The maximum breathing capacity [13] was considered to be the greatest possible quantity of air a

9. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395, 1929.

10. Hickam, J. B., and Frayser, R.: Spectrophotometric Determination of Blood Oxygen, J. Biol. Chem. **180**:457, 1949.

11. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

12. Gaensler, E. A.; Rayl, D. F., and Donnelly, D. M.: Breath Holding Test in Pulmonary Insufficiency: Evaluation of 1,000 Studies, Surg., Gynec. & Obst. **92**:81, 1951.

13. (*a*) Gray, J. S.; Barnum, D. R.; Matheson, H. W., and Spies, S. N.: Ventilatory Function Tests: I. Voluntary Ventilation Capacity, J. Clin. Invest. **29**:677, 1950. (*b*) Methods in Medical Research, edited by G. W. Wright, Chicago, The Year Book Publishers, Inc., 1950, p. 213.

patient could breathe in and out during a 30-second period under constant urging by the observer. In eight instances, it was necessary because of exhaustion of the patient to limit the test to a 20-second period. Expired air during this period was collected in a Douglas bag and subsequently measured in a Tissot spirometer. Results were expressed in terms of total respiratory exchange in one minute. The test was repeated several times, the greatest volume being taken as the correct value.

Walking ventilation [14] was regarded as the amount of air breathed by a patient per minute through a low-resistance valve into a Douglas bag while walking at 2 miles an hour for four minutes. Results were expressed as liters per square meter of body surface area per minute. The lowest result of several tests was the value accepted for each patient.

The so-called "surgical index" is a ratio of the walking ventilation to the maximum breathing capacity. It is believed to be an indication of respiratory reserve.[14]

Arterial oxygen content and carbon dioxide tensions were determined for 11 patients during normal respiration while they were breathing room air and while they were breathing a 15% oxygen mixture. The blood samples were analyzed by the manometric method of Van Slyke and Neill.[11] Blood pH was measured with a Cambridge pH meter and was corrected to 37 C.

Evaluation of Clinical Results.—Each patient was questioned with care preoperatively to determine the degree of limitation of activity which he felt. This was designated by the classification of the American Heart Association. Six weeks after the operation and again at intervals up to the end of a year, the patient was questioned to obtain a subjective evaluation of the activities he felt capable of performing. An attempt to confirm these estimates was made by having the patient climb two flights of stairs as fast as possible. Observations were made on the patient's sensation of exhaustion, the speed of climbing, and changes in respiratory and pulse rate. The clinical results were then graded as "excellent," "good," "fair," or "poor." An "excellent" result was considered one in which the patient was capable of full activity to any extent he might desire and was able to live a completely normal life. Such patients were able to make the stair-climbing test with only a moderate rise of pulse rate and respiration. Values returned to resting levels within three minutes. It was felt that a patient had a "good" result if he could go about his daily work without limitation except in attempts to perform strenuous physical work. Such patients climbed stairs without difficulty, although at a slower rate. Afterward the pulse and respiration were rapid, but they usually returned to normal after three to eight minutes. A patient with a "fair" result was improved and able to lead a restricted life in comfort but was unable to undertake any exercise other than walking. The stair climb was made with some difficulty and some resulting dyspnea. When the patient was unimproved by the operation, the clinical result was considered "poor."

RESULTS

Lung Biopsies.—Of the specimens examined, the lung of only one patient (E. B.) was considered to be normal. Intimal proliferation was present to various degrees in the pulmonary arterioles of the remainder of the patients. In the majority this was the predominant change, varying from minimal proliferation, as in Figure 1,

14. Gaensler, E. A., and Carter, M. G.: Ventilation Measurements in Pulmonary Emphysema Treated with Pneumoperitoneum, J. Lab. & Clin. Med. **35**:945, 1950.

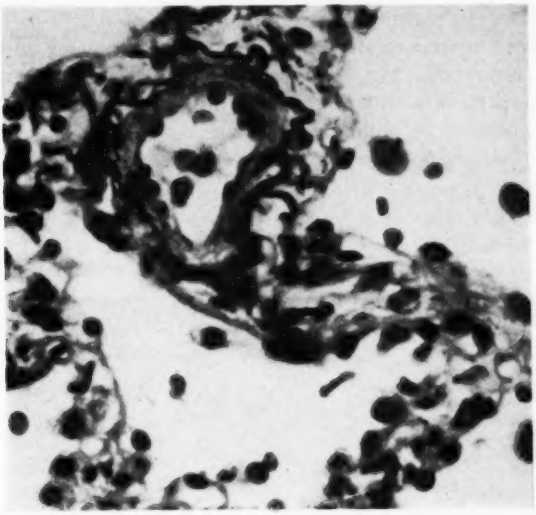

Fig. 1.—Section of lung showing relatively normal small pulmonary arterioles (50μ) with single elastic membrane and slightly thickened intima. Note slight chronic passive hyperemia with alveolar-wall thickening. Weigert's elastic-tissue stain; × 245.

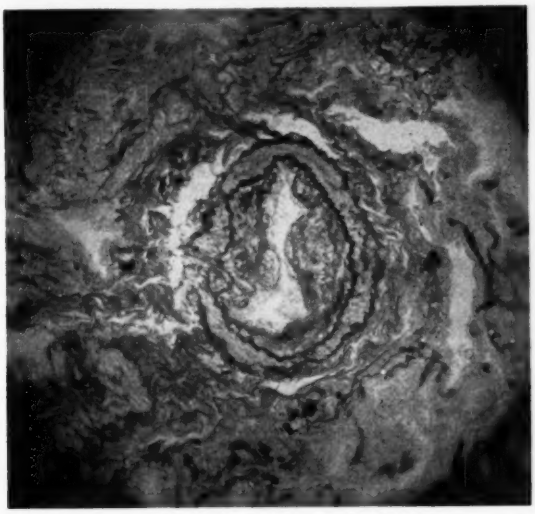

Fig. 2.—Small pulmonary artery (150 to 200μ). Internal and external elastic membranes delineate moderately thickened media. Intima is markedly thickened and lumen narrowed to a slit. Weigert's elastic-tissue stain; × 90.

to a marked thickening, as in Figure 2. Medial hypertrophy was present to some extent in 9 of the 16 patients. Hypertrophied smooth-muscle cells of the media were best outlined in sections stained for elastic tissue showing an internal and an external elastic membrane (Fig. 3). Fibrosis in the media was found to be of minor extent and to be present in only three cases. Intimal thickening, on the other hand, consisted predominantly of proliferating fibrous tissue (Fig. 2). This was accompanied in some instances by inward duplication of the inner elastic membrane.

The degree of pulmonary arteriolar sclerosis is best expressed as the lumen-to-wall ratio (L/W). This value is given for each patient in Table 1. In this series of 16 patients with mitral stenosis the L/W ratio ranged from 1.10 to 4.23. The

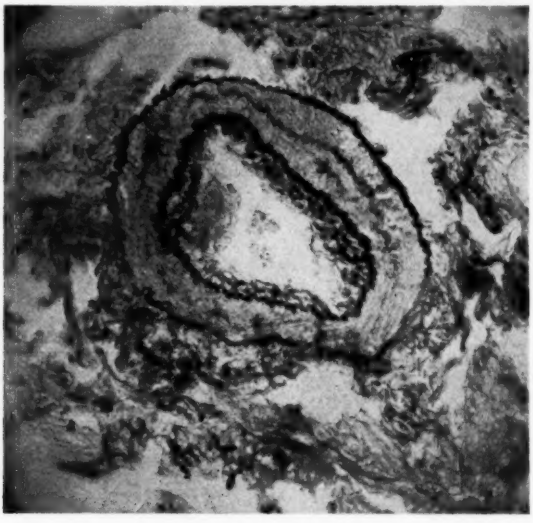

Fig. 3.—Small pulmonary artery (250μ maximum diameter). Media is markedly and irregularly thickened, and intima is moderately thickened. Weigert's elastic-tissue stain; × 120.

average age of these patients was 36.2 years. The L/W ratio of the control series of five patients without pulmonary or cardiac disease ranged from 4.38 to 7.58, with an average of 6.37. The average age of the controls was 38.1, or 2 years more than that of the group under study. The lowest value, 4.38, in the control series was found in a 50-year-old man whose pulmonary arterioles showed slight intimal thickening.

Despite preoperative attempts by medical methods to relieve the patients of excess water, all but 3 of the 16 lung specimens showed slight to moderate chronic passive hyperemia (Fig. 1) with pigment-containing macrophages, "heart failure cells," present in the alveoli. The alveolar walls in these specimens were slightly thickened. Masson's trichrome stain revealed that the thickening consisted of a slight thickening of the capillary basement membrane together with fine strands of fibrous tissue around the capillaries. The actual amount of septal fibrosis was not marked in any case. From inspection of the sections one would expect it to be of little or no functional significance, since this fibrosis was of irregular patchy distribution.

Cardiac Catheterization.—A summary of data on each patient is presented in Table 1. Resting pulmonary arteriolar resistance was calculated from these data for each patient by the formula [15]

$$R \text{ (dynes sec./cm.}^{-5}) = \frac{PA - PC}{CO \text{ (cc./sec.)}} \times 1{,}332$$

where

R = resistance
PA = pulmonary arterial pressure
PC = pulmonary capillary pressure
CO = cardiac output in cc./sec.

This value was found to bear little relationship to the L/W ratio or the degree of arteriolar sclerosis, as illustrated in Figure 4. From data obtained during exercise it was found that arteriolar resistance rose above resting levels in all the patients. No correlation between the extent of this rise and the L/W ratio was found. Data available on nine patients catheterized six weeks postoperatively indicate that arteriolar resistance fell in all, ranging from 38 to 74% of the preoperative level.

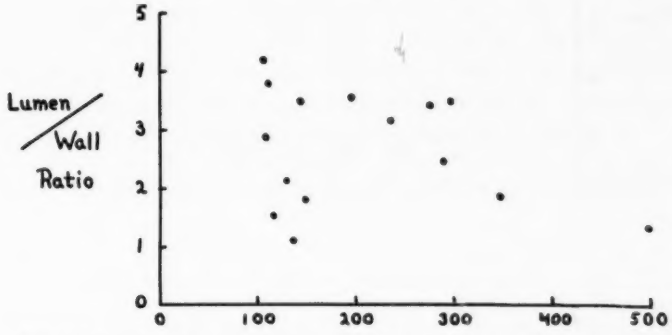

Fig. 4.—Relationship of pulmonary arteriolar resistance to lumen-to-wall ratio of pulmonary arterioles in mitral stenosis.

TABLE 2.—*Relationship of Arteriolar Sclerosis to Preoperative and Postoperative (Six Weeks) Arteriolar Resistance*

Degree of Sclerosis	No. of Cases	Lumen-to-Wall Ratio, Average	Average Arteriolar Resistance	
			Preoperative	Postoperative
Moderate	4	3.6 (2.9-4.2) *	148 (103-290)	97 (40-143)
Severe	5	1.6 (1.1-2.5)	287 (118-680)	176 (81-452)

* The figures in parentheses are the ranges of values.

The highest value found postoperatively was 452 dynes sec./cm.$^{-5}$, for Patient 8. Table 2 indicates that patients with the greater arteriolar-wall thickness had a higher average arteriolar resistance than those with less severe changes. After commissurotomy there was a proportionate fall in the calculated pulmonary arteriolar

15. Fowler, N. O., Jr.; Westcott, R. N., and Scott, R. C.: Pulmonary Artery Diastolic Pressure: Its Relationship to Pulmonary Arteriolar Resistance and Pulmonary "Capillary" Pressure, J. Clin. Invest. **31**:72, 1952.

resistance of each group. Two patients who had severe arteriolar changes and were recatheterized a year after operation showed further diminution of both pulmonary-artery pressure and arteriolar resistance.

No relationship was found between the degree of arteriolar-wall thickening, as indicated by the L/W ratio, and the pulmonary capillary pressure or pulmonary arterial pressure at rest. The latter comparison is illustrated in Figure 5. However, when the lumen-to-wall ratio of each patient was compared with a product of the pulmonary arterial pressure times the duration of respiratory symptoms, there was a significant correlation, the coefficient of correlation being 0.76. This relationship is shown in Figure 6.

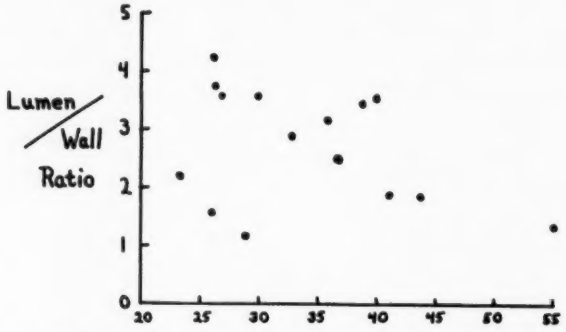

Fig. 5.—Relationship of pulmonary arterial pressure to lumen-to-wall ratio of pulmonary arterioles.

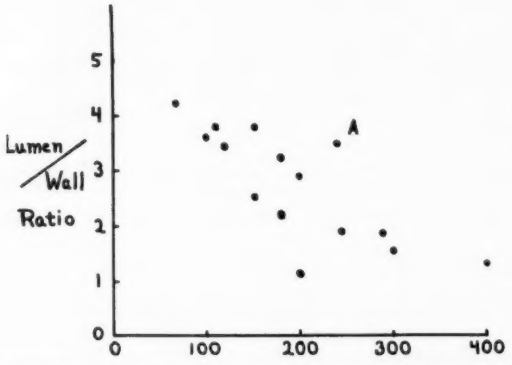

Fig. 6.—Correlation of lumen-to-wall ratio (degree of arteriolar sclerosis) and product of pulmonary intravascular pressure times duration of elevated pressure; coefficient of correlation, 0.76.

Pulmonary-Function Tests.—Three patients were found to have marked limitation of the maximum breathing capacity, as shown in Table 1; Patient 4, 53%, Patient 8, 52%; and Patient 16, 49%, of accepted normal for each individual.[13b] The last of these had severe asthma. The remainder of the patients had maximum breathing capacities of 75% or better. In one (Patient 14) it was 104% of normal. No correlation between maximum breathing capacity and the state of the arterioles or the degree of chronic passive hyperemia was found.

The walking ventilation, or respiratory exchange per minute while the patient was walking at 2 miles an hour, was within normal limits in all but two patients, Patients 4 and 8. Calculation of the "surgical index" (walking ventilation divided by maximum breathing capacity) indicates that all but the three patients with markedly depressed maximum breathing capacity were in the so-called "good-risk range" (a surgical index of 0.10 to 0.20).[14]

The vital capacity ranged from 69 to 104% of normal, as shown in Table 1. It bore little relationship to the degree of arteriolar change present in the lungs. On the other hand, depression of vital capacity was related to the amount of chronic passive hyperemia present, as may be seen in Table 3.

TABLE 3.—*Effect of Chronic Passive Hyperemia on Pulmonary Function (Vital Capacity and Arterial Oxygen Saturation)*

Chronic Passive Hyperemia	No. of Cases	Vital Capacity, % of Normal		Average Arterial O_2 Saturation Respiratory Mixture	
		Range	Mean	Air	15% O_2
None	3	86-99	91	93%	91%
Slight	9	75-102	86	92%	86%
Moderate	4	69-86	81	89%	81%

The carbon dioxide tension of the arterial blood of 11 patients tested preoperatively was between 43 and 47 mm. Hg, a range considered to be within normal limits. The arterial oxygen content, expressed as percentage of the saturation level, ranged preoperatively while the patient was at rest and breathing room air from 86 to 95%. The low values seen in Table 1 were found in patients with the more marked chronic passive hyperemia of their lungs. When patients were given a 15% oxygen mixture to breathe, those with moderate chronic passive hyperemia were found to show considerably more unsaturation than those with only slight hyperemia. This fact is brought out in Table 3. Only a slight fall (3%) in the percentage of oxygen saturation of the arterial blood was found in patients with no hyperemia under these conditions.

Clinical Results of Commissurotomy.—Seven patients obtained "excellent" results from the operation. One of these (Patient 8, Table 1) required six months to obtain her maximum benefit. On the other hand, D. J. (Patient 1) and J. K. (Patient 6) took strenuous jobs within two months and were able to compete effectively with normal people. "Good" clinical results occurred in six patients. Some have shown continuing improvement, particularly Patients 4, 5, and 7. Patient 10, L. S., probably would have had an excellent result had it not been for residual weakness resulting from a preoperative cerebrovascular accident. Patients 9 and 11 were considered to have had only "fair" results. R. W., Patient 9, had a preoperative mild aortic stenosis and regurgitation. Shortly after the operation he was much improved, but he has slipped back, both clinically and according to estimation of pulmonary vascular pressure, which rose slightly from six weeks to a year after the surgical procedure. His left ventricle showed an increase in size from the preoperative measurement by x-ray examination of the chest. I. S., Patient 11, apparently made a good recovery, but suddenly, four weeks postoperatively, a

tachycardia developed which has been difficult to control. This resulted in both right and left failure. However, the heart of this patient appears no larger by x-ray examination than it was preoperatively.

Table 1 shows that there is little relationship between the clinical result of the operation and the state of the pulmonary arterioles or the degree of chronic passive hyperemia in the lung specimens from each patient.

COMMENT

Examination of lung specimens from 16 patients operated upon for relief of the symptoms of mitral stenosis revealed vascular changes in the lungs similar to those described by Parker and Weiss,[2] Larrabee, Parker, and Edwards,[3] and Henry.[5c] Yet it must be emphasized that these authors obtained their material from patients who died of the disease, while this report concerns biopsy specimens from the lungs of living patients with various degrees of physical limitation. The severe necrotizing arteriolitis and alveolar septal fibrosis described by Parker and Weiss were found in none of the patients reported on here. It is of interest that Larrabee and Edwards found significant narrowing of the arterioles in only 15 of their 20 patients, whereas all but one of this series showed a significant decrease in the lumen-to-wall ratio. This fact would be difficult to explain were it not that a number of their patients were young (youngest, 22 years of age), and these changes may not have had time to develop. They found medial hypertrophy to be the predominant feature of their series, in contrast to Henry, who found it in only 40% of his series of 105 autopsies. Our findings agree with the Henry's. Intimal proliferation of various degrees was found in all but one of the biopsy specimens.

Parker and Weiss emphasized that the vascular changes were more pronounced in the lower portion of the lungs of their patients. Therefore, the specimens were removed from the lower lobe in the majority of our patients. When such removal was not practicable, the specimen was taken from the lingula of the upper lobe in an attempt to demonstrate the most pronounced vascular sclerosis in each patient.

Welch and Kinney [4] showed that with each decade of advancing age, in persons with normal hearts and lungs, progressively more arteriolar sclerosis appeared. To be sure that the arteriolar sclerosis observed in our 16 patients was more than would be expected at a given age, a control series of lungs were examined with an age range and an average age similar to those of the patients who were operated upon for mitral stenosis. It is of interest that the oldest control, aged 50 years, had a slight thickening of the intimal layer but had a lumen-to-wall ratio of 4.38. This is higher than the lumen-to-wall ratio of any of the patients with mitral stenosis and at least 23% higher than all but one.

Several authors [16] suggest that arteriolar resistance to blood flow in the lung should be increased by thickening of the arteriolar walls. This should make the walls less distensible and cause a greater impedance to the passage of blood. Figure 4 indicates that in this series such a correlation did not exist. The value arteriolar

16. Edwards, J. E., and Burchell, H. B.: Multilobar Pulmonary Venous Obstruction with Pulmonary Hypertension: "Protective" Arterial Lesions in Involved Lobes, A. M. A. Arch. Int. Med. **87**:372, 1951. Borden, C. W.; Ebert, R. V.; Wilson, R. H., and Wells, H. S.: Pulmonary Hypertension in Heart Disease, New England J. Med. **242**:529, 1950. Parker and Weiss.[2]

resistance in the lung is open to criticism in that a slight error in measurement of the left auricular pressure as reflected by the "pulmonary capillary pressure" [17] can result in relatively large errors in the calculated values for resistance.

The decrease in pulmonary arteriolar resistance observed in nine patients subjected to cardiac catheterization postoperatively is in conformity with the observations of Dexter [18] and Draper and associates.[19] In this series a decrease occurred regardless of the condition of the arterioles. This observation is in accord with the findings of Fowler, Wescott, and Scott [15] that the pulmonary arteriolar resistance varied directly in proportion to either the pulmonary arterial pressure or the pulmonary capillary pressure.

A variety of factors have been implicated in the development of arteriolar sclerosis in the lung. Age appears to create this change normally.[20] Abnormally high pulmonary arterial pressure was believed to be the cause by Parker and Weiss. But there appears to have been little correlation in our patients, as shown in Figure 5, between the degree of wall thickening and the elevation of pulmonary arterial pressure. Baranofsky, Haddy, Ferrin, and Borden [21] mention that time is required for elevated pressure to cause arteriolar sclerosis. It seems logical to consider arteriolar sclerosis as the product of abnormally high intravascular pressure and the duration of the high pressure. To test this idea, the onset of the pulmonary hypertension in our patients was taken as the time when respiratory symptoms began. That this is a reasonable assumption is suggested by the presence in our clinic of five patients with clinically diagnosed mitral stenosis who have not been operated upon because they have no symptoms and only slightly elevated pulmonary pressures. Baranofsky and associates believe that in man symptoms begin at mean pressures as low as 20 mm. Hg in the pulmonary artery. If it be assumed, then, that the duration of symptoms is about equal to the duration of elevated pressure, an interesting correlation is obtained, as shown in Figure 6, between the product of duration times the pressure and the arteriolar thickening. This observation makes three elements important in the production of pulmonary arteriolar sclerosis: (1) age, (2) elevated pressure, and (3) duration of elevated pressure.

Gray and associates [13a] state that voluntary ventilation capacity, as they refer to maximum breathing capacity, is a function of three factors: (1) obstruction, (2) distensibility of the lung, and (3) power "to drive the bellows." Probably the last factor was the most important cause of the minimal depression of maximum

17. Hellems, H. K.; Haynes, F. W.; Dexter, L., and Kinney, T. D.: Pulmonary "Capillary" Pressure in Animals Estimated by Venous and Arterial Catheterization, Am. J. Physiol. **155**:98, 1948. Haddy, F. J.; Ferrin, A. L.; Hannon, D. W.; Alden, J. F.; Adams, W. L., and Baranofsky, I. D.: An Evaluation of Wedge Pressure in Dogs Under Conditions of Normal and Elevated Pulmonary Vascular Pressures, to be published. Ankeney, J. L.: Interrelations of Pulmonary Arterial, "Capillary" and Left Atrial Pressures Under Experimental Conditions, Am. J. Physiol. **169**:40, 1952.

18. Dexter, L.: Pathologic Physiology of Mitral Stenosis and Its Surgical Implications, Bull. New York Acad. Med. **28**:90, 1952.

19. Draper, A.; Heimbecker, R.; Daley, R.; Carroll, D.; Mudd, G.; Wells, R.; Faholt, W.; Andrus, E. C., and Burg, R. J.: Physiologic Studies in Mitral Valvular Disease, Circulation **3**:531, 1951.

20. Welch and Kinney.[4] Henry.[5c]

21. Baranofsky, I. D.; Haddy, F. J.; Ferrin, A. L., and Borden, C. W.: Cardiopulmonary Dynamics of Mitral Stenosis: A Clinical and Experimental Study, read before the Society of University Surgeons, St. Louis, 1953, to be published.

breathing capacity found in the majority of our patients. Ventilating at a maximal rate for 30 seconds is strenuous physical work. Four patients became so exhausted that it was deemed advisable to estimate their capacity to ventilate on the basis of a 20-second test. Of the three patients who exhibited marked limitation by this test, one had had a previous cerebral accident, one was an asthmatic, and the last was a Class IV patient who became exhausted easily. It the latter two patients, there was a concomitant depression of vital capacity, and both showed moderate chronic passive hyperemia in their lung specimens. This hyperemia may have had some effect on the distensibility of the lung. Yet other patients showing comparable hyperemia in their lungs had nearly normal maximum breathing capacity. The lack of correlation of the results of this test with the pulmonary pathological findings suggests that in these cases the result of the test was dependent upon the limitation imposed by the heart on the patient's capacity to perform the physical work of the test.

The "walking ventilation" test is a measure of the ventilation necessary to perform mild work. Failure of diffusion of oxygen or carbon dioxide across the alveolar membrane results in an abnormally high ventilation during this test.[22] Yet in only two patients were elevated values found. One had normally saturated blood at rest and while breathing a 15% oxygen mixture; the other did not. Similarly, one showed very slight hyperemia in the lung, and the other did not. In this series, there appears to have been little relation of the state of the lung to the results of the walking ventilation tests.

Of the pulmonary-function tests the vital capacity appears to be more closely related to the pathological findings in the lung. As shown in Table 3, the degree of chronic passive hyperemia affects the vital capacity adversely. This observation is in agreement with Peabody's concept.[23]

Parker and Weiss believed that cyanosis in patients with mitral stenosis was due to fibrosis of the alveolar septa and to enlargement of the pulmonary capillaries. These changes were not found to any marked extent in the biopsy specimens of this series. Nevertheless, two of the patients exhibited some unsaturation of arterial blood while breathing air. Both had moderate chronic passive hyperemia. This was not true of all the patients with the same degree of chronic passive hyperemia. However, when the patients were given 15% oxygen to breathe, there was more arterial unsaturation in the patients with greater degrees of chronic passive hyperemia than in those whose lungs were normal or nearly so. Perkins and associates [24] made similar observations on patients with mild degrees of emphysema. From these findings it appears that tests of the vital capacity and oximetry studies may be the most useful tests in evaluating the functional state of the lung in patients with mitral stenosis.

Surgery for mitral-valve stenosis has largely given gratifying clinical results in the relief of symptoms and the restoration of function.[25] Such has been the

22. Footnote 13*b*. Gaensler and Carter.[14]

23. Peabody, F. W.: Cardiac Dyspnea, Harvey Lect. **12**:248, 1917.

24. Perkins, J. F., Jr.; Adams, W. E.; Christoff, N.; Flores, A., and Webber, W. W.: Tests of Pulmonary Function Utilizing Recording Oximeters, Fed. Proc. **11**:121, 1952.

25. Janton, O. H.; Glover, R. P.; O'Neill, T. J. E.; Gregory, J. E., and Froio, G. F.: Results of the Surgical Treatment for Mitral Stenosis, Analysis of 100 Consecutive Cases, Circulation **6**:321, 1952. Harken and associates.[7]

experience with the patients of the group under study. "Excellent" and "good" clinical results have occurred regardless of the state of the pulmonary vasculature. The unsatisfactory results, in Patients 9 and 11, Table 1, were apparently much more dependent upon factors within the heart itself, which interfered with its function.

SUMMARY AND CONCLUSIONS

Lung specimens were obtained from 16 patients operated upon for mitral stenosis. The vascular changes observed were compared with the results of preoperative and postoperative cardiac catheterization and pulmonary-function studies, as well as with the ultimate clinical result.

Definite thickening of the arteriolar walls with intimal proliferation was found in all but one of the lungs examined. Medial hypertrophy was a less prominent feature, occurring in only 9 of the 16 cases. Slight to moderate chronic passive hyperemia was present with but three exceptions.

The degree of sclerosis was expressed as a lumen-to-wall ratio. For these patients this value ranged from 1.10 to 4.23. In a control series, of the same age range, the lumen-to-wall ratio varied from 4.38 to 7.58.

The lumen-to-wall ratios for the arterioles found in the biopsy specimens did not correlate with either the pulmonary arterial pressures or the calculated pulmonary arteriolar resistances.

There was a significant correlation between the lumen-to-wall ratios and the product of pulmonary arterial pressure times the duration of symptoms. This fact suggests that pressure and the duration of abnormally high pressure are both factors responsible for the occurrence of pulmonary arteriolar sclerosis.

The extent of decrease in vital capacity is directly related to the degree of chronic passive hyperemia observed.

During breathing of a 15% oxygen mixture, the arterial oxygen saturation was lower in patients with moderate chronic passive hyperemia than in those with normal or slightly hyperemic lungs.

The clinical outcome of mitral commissurotomy in our experience, as in other reported series, is usually good. Patients with severe pulmonary arteriolar sclerosis may take six months or more to obtain maximum benefit. Poor results appear not to be caused by the state of the pulmonary vasculature but by factors within the heart which interfere with its normal function, such as concomitant valvular disease or myocarditis.

DISCUSSION

DR. HENRY SWAN, Denver: I should like to compliment Dr. Clowes on the extremely important and interesting study which he is conducting. Also, we must recognize, I am sure, that he must consider this study in the form of a preliminary report, because, clearly, it is going to take a considerable period of time after commissurotomy to be able to evaluate whether or not changes which are present in the lung at the time of the operation are reversible. I know that he has in mind the follow-up of these patients, obtaining repeated data after a year or more.

Now it seems rather clear that, to a large extent, the less major changes in the pulmonary tree—and I think he has already demonstrated this—do indeed reverse rather rapidly from a physiologic point of view. The question, of course, will be: Will the more major changes reverse? If they do, then the operation will be beneficial for those patients who clinically are classed preoperatively in Group IV.

My colleagues and I have been interested in the same problem. We have been withholding our postoperative evaluation until one year has elapsed in order to allow time, we hope, for the evaluation of the regression of the severer types of lesions. This would be extremely important to know with certainty because, for example, it might be possible that lung biopsy would be a good criterion for the potential benefit of the operation.

I should like to show two slides.

[Slide] This slide merely shows the classification which we are using—a rather gross one—giving the degree of vascular change which one may see in the lung biopsy. The medial hypertrophy begins to cause the decrease in lumen-to-wall ratio, as Dr. Clowes mentioned. Later, intimal proliferation and extensive degeneration of the vessel are added.

[Slide] We have just these few patients who have now had their one-year catheterization, and the results are merely tabulated in gross form here. The first column on the left shows our evaluation of the degree of vascular change as correlated with postoperative improvement in the Grade III and Grade IV groups. We had only one patient with Grade IV changes in the vessels. This particular patient had poor clinical and poor catheterization results.

We feel that the cardiac output, particularly the capacity of the patient to raise cardiac output on exercise, also appears to parallel rather closely the degree of change in the blood vessels of the lung.

CHRONIC LUNG ABSCESS

Fifteen Years of Change

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DURING the 15-year period covered by this presentation there has occurred a progressive change in the surgical therapy of chronic lung abscess. Resectional therapy was sporadically used in the early years of this study. Its use has increased during this period, until at present excisional surgery constitutes the treatment of choice in the majority of cases. This change has paralleled the interest in and the development of thoracic surgery, assisted by remarkable strides in anesthesia, blood replacement, and antibiotic therapy. This analysis substantiates the trend and supports the acceptance of resection treatment as a rapid means of cure accompanied by a low morbidity and mortality rate. A striking reduction in the length of hospitalization is evident.

This study is not concerned with the surgical therapy of acute lung abscess, which has also undergone change since the extensive work of Neuhof.[1]

In the 15-year interval between 1937 and 1952, there were 128 consecutive patients with chronic lung abscesses admitted to the University of Iowa Hospitals. In this analysis these patients are divided into three general groups: (*a*) those with no surgical therapy, 50; (*b*) those with surgical drainage, 31, and (*c*) those with pulmonary resection, 47. Fifty patients receiving no surgical therapy are included for comparison. All patients showed a lung abscess on roentgenographic examination of the chest. Patients whose primary disease was bronchiectasis are excluded.

CAUSATIVE FACTORS

Of the patients, 63, or 49.1%, gave a history of "pneumonia" preceding the onset of their chronic illness. In the remainder, including 14 patients with postoperative abscesses, the causative factors were distributed as shown in Table 1.

Of the postoperative abscesses, 4 occurred following tonsillectomies, and the remaining 10 were distributed among a variety of major surgical procedures.

Read at the Tenth Annual Meeting of the Central Surgical Association, Chicago, March 6, 1953.

From the Department of Surgery, Division of Thoracic Surgery, State University of Iowa College of Medicine.

1. Neuhof, H.: Acute Putrid Abscess of the Lung, Surg. Gynec. & Obst. **80**:351, 1945. Neuhof, H., and Touroff, A. S. W.: Acute Putrid Abscess of the lung, ibid. **63**:353, 1936.

Aspiration of the following foreign materials accounted for lung abscesses: vomitus, 8 (frequently in patients with an alcoholic history); peanuts, 3; timothy head, 1; soot, 1; water aspirated while swimming, 1.

The four patients listed as having bronchiectasis showed chronic bronchiectatic changes in the lobe containing a well-developed chronic lung abscess.

TABLE 1.—*Causative Factors*

	Patients, No.
Postpneumonic	63
Unknown	28
Postoperative	14
Aspiration of foreign body	14
Pulmonary infarct	4
Bronchiectasis	4
Brucellosis	1
Total	128

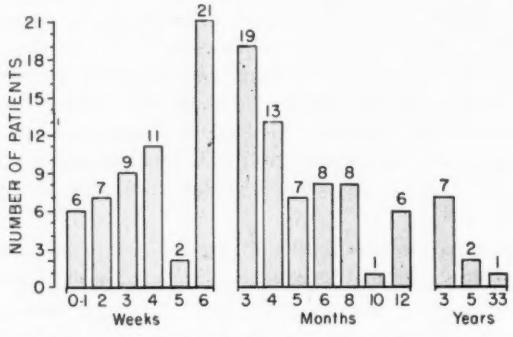

Chart 1.—Showing distribution of duration of symptoms for all patients.

TABLE 2.—*Incidence of Common Symptoms*

	Patients, No.	Percentage of Total
Productive cough	123	96.0
Chest pain	120	94.0
Symptoms of chronic sepsis	128	100.0
Hemoptysis	52	41.4
Osteoarthropathy	7	5.4

SYMPTOMS

Patients with chronic lung abscess present a farily uniform history after the development of their lesions. Over 90% of the 128 patients exhibited chronic productive cough, pleuritic-type chest pain, and evidence of chronic sepsis. Fifty-two, or 41.4%, experienced hemoptysis. Osteoarthropathy was noted in seven, or 5.4%. Five of these patients had the disease for over eight months.

Fifty-three, or 41.4%, of the patients entered the hospital with symptoms of 6 to 12 weeks' duration. Sixteen patients, or 12.5%, had the above symptoms for periods of over one year. The longest case history dated back 33 years. Chart 1 depicts the duration distribution and Table 2 the incidence of symptoms.

AGE AND SEX

The patients ranged in age between 4 and 82 years. The largest group of patients, 33 in number, were between 41 and 50 years of age. The distribution is shown in Chart 2. Of the patients, 100, or 78.1%, were males, while 28, or 21.9%, were females. The reason for this 4:1 male preponderance is not apparent.

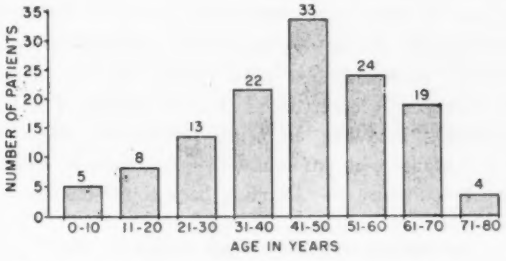

Chart 2.—Showing age distribution of the 128 patients.

TABLE 3.—*Location of Abscesses*

Left	No.	Right	No.
Upper lobe	18	Upper lobe	34
Lower lobe	20	Middle lobe	15
Superior segment	4		
Upper and lower lobes	2	Lower lobe	26
		Superior segment	7
		Upper and lower lobes	2
Total	44	Total	84

TABLE 4.—*Culture Incidence of Various Micro-Organisms*

	No. of Times
Beta hemolytic Streptococcus	51
Hemolytic Staphylococcus	16
Alpha hemolytic Streptococcus	14
Hemophilus influenzae	7
Pseudomonas aeruginosa	7
Escherichia coli	6
Staphylococcus albus	5
Aerobacter aerogenes	4
Candida albicans	5
Pneumococcus	4
Proteus vulgaris	3
Actinomyces	3
Klebsiella pneumoniae	1

LOCATION OF LESION

Of the lesions, 84, or 65.6%, occurred on the right side; 44, or 34.4%, on the left. The upper and lower lobes shared nearly equally in the distribution. The distinctly preponderant incidence on the right side is evident. The dominance of the right side is attributed to the larger alveolar surface and greater ease of aspiration through the more nearly straight right main-stem bronchus. Table 3 shows a break-down of the lobar distribution.

BACTERIOLOGIC STUDIES

Beta hemolytic Streptococci were isolated from the sputa of 51, or 39.8%, of the patients. Both aerobic and anaerobic culture techniques were utilized. In one patient the blood culture was positive for one of the Brucella organisms. The number of times each of the commoner micro-organisms was recovered is indicated in Table 4.

DIAGNOSIS

All of the 128 patients utilized for this analysis showed a definite lung abscess on roentgenography. Bronchograms were utilized in the majority of patients. Radiopaque dye infrequently entered the abscess cavities. The history of chronic pulmonary suppuration following an acute respiratory illness was consistently present. This is in contrast with patients with bronchiectasis, most of whom give a history of pulmonary suppuration extending back to childhood.

ANTIBIOTIC THERAPY AND CHEMOTHERAPY

The use of the sulfonamides was well established shortly after the beginning of the 15-year period of this study. Antibiotics were routinely used in the last one-half of the study period, according to the type of bacterial flora.

A penicillin-streptomycin combination was frequently used in the resected series after 1945. Its use was largely confined to a brief preoperative and postoperative period. Only occasionally has it been necessary to resort to other antibiotic medication. Recent instances of insensitivity constitute the majority of these situations.

TYPE OF SURGICAL THERAPY

In the group of 31 patients treated by drainage procedures, 15 required multiple operations. An indication of the multiplicity of procedures can readily be appreciated from the following data:

	Patients, No.
2 drainages	9
1 drainage and thoracoplasty	1
3 drainages, Estlander, decortication	2
3 drainages, 2 unroofings, skin graft	1
5 drainages, 3 skin grafts	1
4 drainages	1

Among the 47 patients with resection, 6 had previously received thoracotomy drainages. Excisional surgery was performed as indicated:

	Patients, No.
Lobectomy	36
Segmental resection	6
Pneumonectomy	1
Multiple and/or bilateral segmental resections	4

In the majority of these patients and in all those operated upon after 1945, resection was done with use of the individual ligation technique. Fine wire bronchial closure was used until 1949. Since that time interrupted nonabsorbable surgical (silk) suture technique has been employed. Anterior and posterior intercostal drainage tubes were used and these were connected to underwater drainage seal bottles.

LENGTH OF HOSPITALIZATION

The patients receiving no surgical therapy required an average hospital stay of 41 days; the drainage group, 76 days, and the resection group, 43 days. The distribution is depicted in Chart 3. This Chart illustrates the entire hospitalization period of each group. The postoperative hospitalization of the drainage group was considerably prolonged. As can be seen from the Chart, many of the patients requiring no surgical therapy were either well on the way to recovery or moribund at the time of admission. The postoperative hospitalization in the uncomplicated cases with resection averaged 8 to 10 days, indicating the very considerable reduction in hospitalization required by this group. Many patients treated by multiple-drainage and collapse procedures required several admissions, with aggregate hospitalization periods in excess of three to four months.

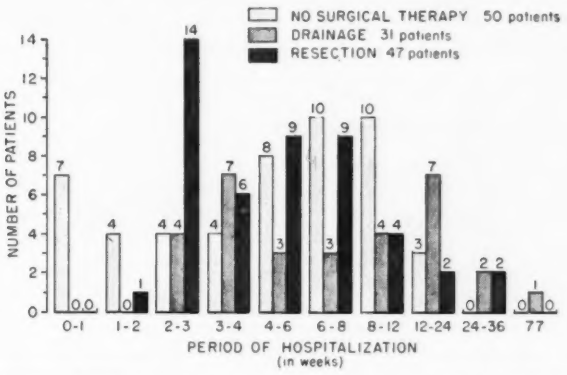
NO SURGICAL THERAPY 50 patients
DRAINAGE 31 patients
RESECTION 47 patients
NUMBER OF PATIENTS
0 2 4 6 8 10 12 14
0-1 1-2 2-3 3-4 4-6 6-8 8-12 12-24 24-36 77
PERIOD OF HOSPITALIZATION
(in weeks)

Chart 3.—Showing distribution of the entire hospitalization period for each group of patients.

MORBIDITY AND MORTALITY

Among the 50 patients not receiving surgical therapy, 11 died during their hospital stay, making a mortality rate of 22%. Ten of these deaths occurred within a few days of entry in patients admitted in a terminal condition. Pulmonary embolization accounted for the remaining death. Three patients were discharged with x-ray evidence of persistent abscesses. Most of the patients in this nonsurgically treated group had abscesses of a few weeks' duration and did not exhibit the thick-walled fibrotic changes of chronic disease. From this date it is seen that in 14 patients, or 10.9% of the total group, abscesses eventually healed without surgical therapy.

Of 31 patients treated by single and multiple surgical-drainage or collapse procedures, 8, or 25.8%, died during their hospital stay. Five died of inadequate drainage, 1 of hemorrhage into the abscess cavity, 1 of brain abscess, and 1 of pulmonary embolism. After drainage 14 bronchopleurocutaneous fistulae persisted, but three closed prior to the time the patients were discharged from the hospital. Two more fistulae closed after the patients left the hospital, so that nine fistulae were still present on their last follow-up visits.

Among 47 patients with resection, 2, or 4.3%, died in the hospital. One death, due to postoperative intrapleural hemorrhage following a tourniquet lobectomy,

occurred in 1940 in a 30-year-old woman. The other, occurring in 1946, followed middle and right lower lobectomy in a 29-year-old woman. Death was ascribed to a contralateral pneumonitis. There have been no operative or postoperative deaths in the past six years. Bronchopleural fistulae developed in 5, or 10.7%, of the patients in this group. Three of these fistulae closed during the patients' hospital stay. One empyema developed postoperatively but was nearly healed by the time

TABLE 5.—*Morbidity and Mortality of Surgically Treated Patients*

	Morbidity								
		Persistent Bronchopleural-Cutaneous Fistula Following Discharge		Bronchopleural Fistula Closed by Discharge		Empyema		Mortality	
Patients, No.	Persistent Abscess	No.	%	No.	%	No.	%	No.	%
Drainage (31)	1	9	29.0	3	9.7	..	..	8	25.8
Resection (47)	..	2	4.3	3	6.4	1	2.1	2	4.3

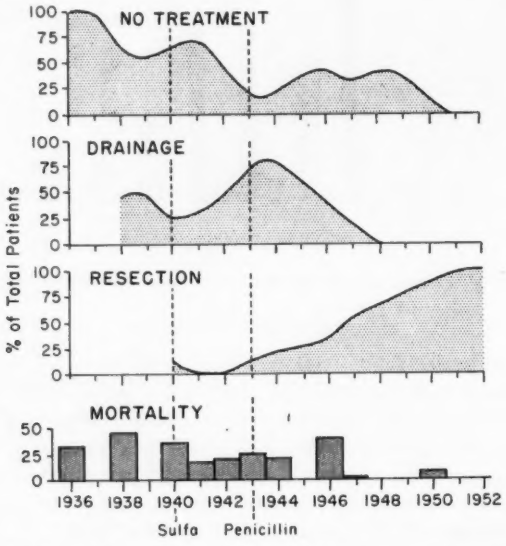

Chart 4.—Showing increasing employment of excisional surgery, with accompanying salutary effect on mortality rate.

of the patient's discharge. This brings the complication rate to 12.8%. In one patient bullous emphysema of the remaining upper lobe developed several years after lower lobectomy. Table 5 depicts the morbidity and mortality rates of all the surgically treated patients.

Chart 4 illustrates graphically the increasing employment of excisional surgery, with an accompanying salutary effect on the mortality rate. Our data fail to show alteration of the over-all mortality coincident to the use of chemotherapy and antibiotics.

SUMMARY AND CONCLUSIONS

The serious nature of this disease process is evident from the mortality rates presented by our data and that of other authors. Eleven, or 22%, of the 50 non-surgically treated patients and 21, or 16.4%, of the entire 128 patients died in the hospital.

The postoperative hospitalization and morbidity of the patients treated by pulmonary resection are significantly decreased as compared with those treated by drainage procedures. The 47 patients with resection experienced a complication rate of 12.8% and a mortality rate of 4.3%. These statistics compare very favorably with data presented by other authors.[2]

We believe that excisional surgery constitutes the treatment of choice in persistent chronic lung abscess. Drainage procedures have been utilized during the past seven years only when resection was contraindicated due to the poor condition of the patient. The frequency with which excavated pulmonary carcinoma mimics benign chronic lung abscess further supports the need for excisional therapy.

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2. Bosher, L. H., Jr.: A Review of Surgically Treated Lung Abscess, J. Thoracic Surg. **21**:370, 1951. Neerken, A. J., and Grow, J. B.: Pulmonary Resection for Lung Abscess, ibid. **18**:738, 1949. Shaw, R. R., and Paulson, D. L.: Pulmonary Resection for Chronic Abscess of the Lung, ibid. **17**:514, 1948. Kent, E. M., and Ashburn, F. S.: Pulmonary Resection for Chronic Lung Abscesses, ibid. **17**:523, 1948. Valle, A. R.: Lung Abscess; Analysis of 244 Cases, Surg. Gynec. & Obst. **81**:278, 1945. Sweet, R. H.: An Analysis of the Massachusetts General Hospital Cases of Lung Abscess Form 1938-1842, ibid. **80**:568, 1945.

ETIOLOGY AND MANAGEMENT OF SPONTANEOUS PNEUMOTHORAX

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ALFRED A. THURLOW Jr., M.D.
SANTA ROSA, CALIF.
AND
KARL P. KLASSEN, M.D.
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CONFLICTING viewpoints are held concerning the management of spontaneous pneumothorax. At the Ohio State University Hospital members of the medical service advocated conservative care consisting mainly of bed rest, while members of the thoracic surgery service preferred surgical intervention. In order to arrive at a definite conclusion as to the best method of treatment of this disease, records of patients with spontaneous pneumothorax admitted to the hospital over the last 10-year period were reviewed. Only 20 cases were found in the records of the Ohio State University Hospital during the 10-year period of 1942 to 1952. These were supplemented by an additional 16 cases for the three-year period 1949 to 1952 from the records of Hurley Hospital, Flint, Mich. Case studies were consecutive and unselected.

ETIOLOGICAL FACTORS

In order to establish a satisfactory definition of spontaneous pneumothorax it was necessary first to review the cases "automatically" included under this diagnosis and then to evaluate their supposed, if not proved, pathogenesis. It was concluded that the entity could best be described as a pneumothorax resulting from a bronchial tree-pleural space communication not established by direct laceration of intervening tissues.

It is difficult in many instances to establish the exact pathogenesis of spontaneous pneumothorax. Had surgery been performed the diagnosis would have been apparent. In 64% of our cases the condition was labeled "idiopathic." Certain factors are known to be of etiological significance, and cases can be classified most conveniently under the following headings:

1. *Structural Cystic Lung Changes.*—Since no definite clinical, gross, or microscopic criteria are as yet evident to differentiate the various cystic alterations found in the lungs, no classification is entirely satisfactory. A simple concept, similar to that of Murphy and Piver,[1] has been used with satisfaction by us:

Read at the Tenth Annual Meeting of the Central Surgical Association, Chicago, March 6, 1953.

From the Division of Thoracic Surgery, the Ohio State University Hospital, Columbus, Ohio, and Hurley Hospital, Flint, Mich.

1. Murphy, J. D., and Piver, J. D.: Cystic Disease of the Lung, Dis. Chest **19**:454-472 (April) 1951.

A. Congenital Cystic Disease: Such cysts are usually lined by bronchial epithelium but may be affected by squamous metaplasia, infection, and so on. They may be single or diffuse. Some contain fluid, but most contain only air. All probably have a bronchial-tree communication, but this is difficult to demonstrate. Infection may be present and a lung abscess or even empyema simulated. Compression of adjacent lung tissue by overdistention of cysts, or infection and collection of secretions within them, accounts for the symptomatology of dyspnea, cough and expectoration, hemoptysis, and chest pain. A history of such symptoms in childhood and adolescence antecedent to a spontaneous pneumothorax suggests this etiology.

Rupture of such cysts occurs when air enters but cannot leave, so that overdistention with thinning of the wall is produced. Rupture eventually occurs with slight trauma, as first described by Hayashi.[2]

We had no cases in our series which could be classified under this etiology (Table 1).

B. Cystic Bronchiectasis: It is uncertain whether this is a congenital or acquired lesion. It is, however, an established entity and may be suspected with basilar localization of cysts. Diagnosis is established by bronchography when a grossly dilated

TABLE 1.—*Etiology*

Condition	Cases, %
Congenital cystic disease	0
Cystic bronchiectasis	0
Inflammation	
Tuberculosis	6
Pneumonia	6
Obstructive emphysema	15
Indirect trauma	9
Idiopathic	64

bronchus is seen communicating with the cyst. Such cysts have a bronchial epithelial lining and usually do not attain great size, because of the associated dilated bronchus. Rupture is rare. Abscess formation followed by rupture into the pleural space and subsequent empyema is seen more commonly, but this, too, is infrequent.

This pathology was not demonstrated in any of our cases, but bronchograms were not made routinely (Table 1).

2. *Inflammation.*—Until 1932 most reports suggested active tuberculosis as the important etiological factor in spontaneous pneumothorax.[3] In all probability this was because most studies emanated from tuberculosis sanatoria. However, subsequent to Kjaergaard's publication [4] in which active tuberculosis was reported as developing in only 1 of 51 cases (and then after later specific exposure), it became evident that active tuberculosis is an infrequent cause.[5] When the two diseases are

2. Hayashi, J.: Über tötlichen Pneumothorax durch Infarkt und Emphysem, Frankfurt. Ztschr. Path. **16**:1-36, 1914.

3. Myers, J. A., and McKinlay, C. A., Editors: The Chest and the Heart, Springfield, Ill., Charles C Thomas, Publisher, 1948, Vol. 1, pp. 239-250.

4. Kjaergaard, H.: Spontaneous Pneumothorax in the Apparently Healthy, Acta. med. scandinav. Supp. 43, pp. 1-159, 1932.

5. Brock, R. C.: Recurrent and Chronic Spontaneous Pneumothorax, Thorax **3**:88-111 (June) 1948.

associated, tuberculous empyema is an almost unfailing sequel, since the pneumothorax results from rupture of a thin-walled subpleural cavity and caseous focus. The lung fields usually show moderate to extensive disease, and there is no great difficulty in diagnosis.

Arrested tuberculosis may be a factor as well, for bleb formation may result from the fibrotic reaction, as with any nonspecific inflammation. This etiology might be suspected when apical or subapical x-ray changes are noted,[5] but it is difficult to establish the diagnosis without microscopic evidence.

Active nonspecific infections such as pneumonia, bronchiectasis, and pulmonary abscess have been associated with spontaneous pneumothorax, but cases of direct relationship are infrequent. In such instances empyema may complicate the picture. It seems likely that these diseases play a greater part indirectly by inducing structural lung changes (i. e., bleb), as suggested by Clagett.[6]

In only two patients (6%) were we able to establish the diagnosis of active tuberculosis. No patient had a history or x-ray evidence of healed tuberculosis (Table 1).

TABLE 2.—*Results of Skin and Sputum Tests for Tuberculosis*

Test	Cases, %
Skin	
Positive	8
Negative	33
Not done	59
Sputum	
Positive	5
Negative	56
Not done	39

Tuberculin skin tests and sputum examinations were done routinely during the past two years in all cases. The results of these (Table 2) lend support to the fact that tuberculosis is an infrequent cause of spontaneous pneumothorax.

Two patients (6%) showed x-ray evidence of an underlying pneumonic process following reexpansion of the lung (Table 1), and we assume that this was responsible for the pneumothorax. It is possible, however, that the pneumonia was coincidental or perhaps followed reexpansion.

3. *Emphysema.*—Christie[7] has classified five entities under the heading of emphysema:

(1) Hypertrophic or chronic obstructive.

(2) Acute vesicular associated with acute infections of the respiratory tract.

(3) Localized or compensatory due to atelectasis and fibrosis.

(4) Atrophic or senile.

(5) Surgical or acute interstitial associated with chest injuries or artificial pneumothorax.

6. Clagett, O. T.: Surgical Treatment of Emphysematous Blebs and Bullae, Dis. Chest **15**:669-683 (June) 1949.

7. Christie, R. V.: Emphysema of the Lung, in British Encyclopedia Medical Practice, H. Rolleston, Editor, London, Butterworth & Co., Ltd., 1937, Vol. 4, 508-519.

Only the hypertrophic or chronic obstructive type is considered. This is usually a sequel to asthma, but in some cases the history may be entirely lacking in asthmatic symptoms. It is essentially an obstructive type with incomplete bronchial occlusion allowing the intake of air on inspiration and trapping within the alveoli on expiration. The sequel to such a phenomenon is overdistention and the formation of intrapulmonary bullae or of subpleural blebs.[8] Rupture of such structures is a major factor in the etiology of spontaneous pneumothorax.

Senile or atrophic emphysema, on the other hand, is essentially a phenomenon of overdistention of alveoli by virtue of a dorsal kyphosis with widening of the posteroanterior diameter of the chest and an increase of the intrathoracic volume. Since there is no abnormal increase in intra-alveolar tension, rupture with spontaneous pneumothorax is infrequent.

The diagnosis of asthmatic emphysema was established in five (15%) of our patients. This factor was responsible for most cases in patients over 50 (Table 1).

4. *Trauma.*—Traumatic pneumothorax implies establishment of a communication between the pleural space and the outside air (through either the chest wall or the bronchial tree) by direct tissue laceration (e. g., penetrating wounds, rib fractures). Traumatic spontaneous pneumothorax, on the other hand, implies an indirect mechanism of sudden increase in intrabronchial pressure which ruptures the intervening tissues into the pleural space. Among causes can be included such factors as positive pressure anesthesia, bronchoscopy, playing of a wind instrument, violent cough, exercise, and use of a pulmotor. While it is possible that no underlying lung pathology exists in such instances, it seems probable that subpleural bleb formation is often present. Thus, trauma that would be innocuous to normal lung produces a pneumothorax. It is not within the scope of ordinary diagnosis to prove the existence of such blebs, and unless they appear on routine roentgenograms or the patient comes to thoracotomy, the true mechanism of the disease remains obscure. Slight trauma may be involved in every instance of spontaneous pneumothorax, this being "the final straw that breaks the camel's back." It is fallacious to ascribe fundamental significance to this mechanism.

For only three patients (9%) were we able to obtain a history of such trauma, in each instance paroxysms of violent cough (Table 1). Only one patient had ever played a wind instrument, and he also was the only athlete in the series (track); his spontaneous pneumothorax occurred, however, while he was sitting in a chair. Characteristic activity of other patients included "driving an automobile," "sitting in church," "arising from a chair," "bending over," "reading the comics," "lying in bed," "raising an auto trunk," and "walking." Others have noted a lack of relationship to exertion.[9]

5. *Idiopathic Pneumothorax.*—In most cases of spontaneous pneumothorax the etiology cannot be established. This was true for the majority (64%) of our patients (Table 1).

8. Head, J. R., and Avery, E. E.: Intracavitary Suction (Monaldi) in the Treatment of Emphysematous Bullae and Blebs, J. Thoracic Surg. **18**:761-776 (Dec.) 1949.

9. Hughes, F. A., Jr.; Kraeft, N. H., and Lowry, C. C.: Treatment of Idiopathic Spontaneous Pneumothorax, J. A. M. A. **146**:244-247 (May 19) 1951.

It appears that such patients have small subpleural blebs which cannot be demonstrated by x-ray. These may have arisen from any of the causes listed or from some more obscure pathology.

The two patients in our series who underwent thoracotomy had such blebs clearly demonstrable, although their etiology could not be shown.

RESULTS OF MANAGEMENT

Table 3 indicates the method of management of all patients in this series.

No Specific Treatment.—Fourteen (39%) patients were treated expectantly. Of these two had minimal collapse, of 5% and 15%, and the lung reexpanded uneventfully within a week. Two more had collapse of 25%. Of these, the lung of one had completely reexpanded within three weeks and the patient had returned to work. The other patient was unimproved according to x-ray 12 days after the onset but was discharged from the hospital asymptomatic. (Follow-up was not available.) One patient with 70% collapse had shown no change by x-ray four days later and was referred to the thoracic surgery service for thoracotomy-tube management because of continued symptoms of pain and dyspnea.

TABLE 3.—*Methods of Management*

Method	Cases, %
No specific treatment	39
Thoracentesis	14
Intrapleural needle with water-seal drainage	3
Thoracotomy tube with water-seal drainage	39
Thoracotomy	6

Of the remaining nine patients, the lung of none had completely reexpanded at the time of hospital discharge (up to 35 days) and only two had as much as 80% reexpansion (after 16 days and 35 days).

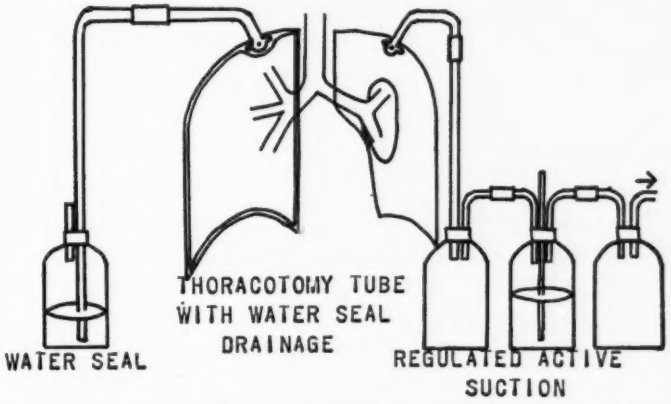
Thoracenteses.—Five patients (14%) were treated by this method. Two of these were eventually referred for the insertion of a thoracotomy tube with water-seal drainage. In one patient a bronchopleural-cutaneous fistula developed and an upper lobe resection was eventually done. One patient with 100% collapse and pulmonary tuberculosis was transferred to a veterans' hospital 11 days after admission, with the lung completely unexpanded despite six needle aspirations. Only one patient recovered uneventfully, the lung being completely reexpanded in six weeks.

Intrapleural Needle Insertion with Water-Seal Drainage.—One patient was treated by this method. Three days after insertion of the needle it came out accidentally, and no further treatment was employed. This patient was hospitalized for 16 days, at the end of which his lung was 95% reexpanded. At the end of four months reexpansion was complete.

Thoracotomy Tube with Water-Seal Drainage.—Fourteen patients (39%) were treated by this method. In all instances the tube was inserted as soon as the patient was seen by the thoracic surgery service and x-rays were available. A Pezzer catheter (size 18 to 26) was introduced into the pleural cavity under local anesthesia through the second anterior intercostal space. If the upper lobe was adherent the tube was placed in the optimum position as indicated by the roentgenogram. The

tube was immediately attached to a single-bottle water-seal drainage. In most instances the tube was removed after 48 to 72 hours. If the lung was clinically reexpanded at this time the tube was clamped and the patient sent to the x-ray department for routine posteroanterior roentgenograms of the chest. The tube was then removed if an x-ray confirmed the clinical impression. Penicillin (200,000 units) and streptomycin (1 Gm.) were introduced into the pleural cavity through the tube both at the time of insertion and at the time of removal. If reexpansion did not occur within 48 hours the single-bottle water-seal drainage was replaced by regulated active suction, as shown in the accompanying illustration.

Two complications were noted in this group. In one patient pleural effusion developed and the tube was not removed for 17 days, at the end of which time the lung was 95% reexpanded. Follow-up x-rays one month later showed only minimal pleural "thickening." The lung of the other patient was completely reexpanded after 48 hours, but a bronchopleural-cutaneous fistula developed when the tube was



Pezzer catheter for intrapleural use, with simple water-seal drainage (left) and regulated active suction (right).

removed. It was believed that the tube had been inserted into the ruptured bleb or had become so situated as the lung reexpanded.

Thoracotomy.—Two patients (6%) eventually came to thoracotomy. One had a spontaneous hemopneumothorax and continued to have hemorrhage despite thoracotomy-tube and water-seal drainage. At surgery bleeding was found to arise from an intercostal artery, apparently at the site where an adhesion had torn simultaneously with development of the pneumothorax. Recovery was uneventful. The lung of the other patient failed to reexpand after multiple thoracenteses and a bronchopleural-cutaneous fistula developed. At surgery the right upper lobe was partially resected and numerous blebs, the largest 2 cm. in diameter, were found. Recovery was uneventful.[10]

Adjunctive Therapy.—In addition to the primary methods of management discussed, the following supportive therapy should be utilized:

10. Since this article was prepared two more patients have undergone thoracotomy, both for recurrent spontaneous pneumothorax. In both instances recovery has been uneventful, and to date no further recurrences have been noted.

Bed Rest: Increase in the depth and rate of respiration was avoided by restriction of activity. Those patients, however, who were treated by thoracotomy tube were allowed wheel-chair privileges with water-seal drainage in operation.

Administration of Oxygen: This is seldom indicated except in the presence of severe cyanosis. Anoxia is due to pulmonary insufficiency, and therapeutic efforts should be directed, therefore, to immediate reexpansion of the lung.

Use of Expectorants: Efforts should be directed to maintaining bronchial secretions thin and watery so that they may be readily expectorated, since cough reflex is already inhibited by pain. Occlusion of the contralateral bronchus by a tenacious mucous plug and subsequent atelectasis may invite disaster. Our patients were given sodium iodide, 1 gm. intravenously, twice daily.

Administration of Antibiotics: Since a bronchopleural fistula is present in all instances, direct communication exists between the outside environment and the pleural cavity. Antibiotics should be given, therefore, both systemically and by aerosol to prevent empyema.

Study for Specific Etiology: Efforts should be made in all instances to establish the factor responsible for the spontaneous pneumothorax before the etiology is considered "idiopathic."

TABLE 4.—*Objectives of Therapy*

Complete reexpansion of lung as soon as possible
Relief of symptoms
Prevention of complications
Minimal hospitalization
Early return to economic productivity

COMMENT

Before an adequate appraisal can be made of the therapy for any disease the objectives of therapy should be clearly defined. These objectives can be concisely stated for spontaneous pneumothorax (Table 4).

1. *Complete Reexpansion of the Lung as Soon as Possible.*—This is axiomatic for collapsed lung from any cause. The longer pulmonary tissue remains collapsed the more difficult it is to reexpand. Pleural effusion, persistent bronchopleural fistula, and empyema occur more frequently if repair of the parenchymal tear is delayed. The most effective way of closing this rent is by reexpansion of the lung so that visceral and parietal pleural surfaces come into contact. The fistula is thus closed by adhesion of the two pleural surfaces at the site of rupture. Closure by coaptation of the edges of the rent in the collapsed state is problematical. Moreover, a rupture so healed is placed under tension as the lung expands, and its edges are apt to separate as reexpansion occurs.

If collapse is minimal (less than 25%) specific treatment is probably unnecessary. The lungs of patients in our series with such minimal collapse reexpanded fully in a relatively short time (maximum three weeks) without surgical intervention.

Thoracentesis has proved ineffective. Evacuation of air from the pleural cavity by this method fails to hold the ruptured bleb against parietal pleura long enough for healing to occur. Moreover, the needle itself may produce trauma to the expanding lung.

Intrapleural insertion of a needle with water-seal drainage overcomes some of the difficulties of simple thoracentesis. However, it is difficult to maintain the needle within the pleural cavity, and further parenchymal damage by the needle as the lung reexpands can occur.

Reexpansion can be most rapidly attained and maintained by use of a thoracotomy tube with water-seal drainage.[11] In most instances physical examination revealed return of breath sounds within several hours. X-rays were usually not taken until 48 hours after insertion of the tube, at which time reexpansion was usually complete. In one instance x-rays taken 20 minutes after the operative procedure revealed 95% reexpansion.

Thoracotomy is indicated for patients whose lungs fail to reexpand with catheter drainage.

2. *Relief of Symptoms.*—The chief symptoms, chest pain and dyspnea, are usually relieved shortly after insertion of a thoracotomy tube. Apprehensive patients in whom symptoms persist despite a reexpanding lung may be safely given narcotics without fear of respiratory depression. This statement does not hold true for patients with collapse.

TABLE 5.—*Percentage of Collapse at Discharge in Relation to Treatment*

Type of Treatment	Collapse at Discharge, %
No specific treatment	34
Thoracentesis	
Only 6% of lungs completely reexpanded	
Thoracotomy tube with water-seal drainage	2.5
55% of lungs completely reexpanded; no patient had more than 10% collapse	

Symptoms persist, however, in patients without specific treatment. Thoracentesis may give momentary relief followed by recurrence as collapse recurs.

3. *Prevention of Complications.*—Tension Pneumothorax: Since evacuation of air by any means available is absolutely indicated for tension pneumothorax, discussion of alternative methods of treatment is unnecessary. In acute emergencies air may be most rapidly removed by thoracentesis, with syringe or water-seal drainage. This drainage should be replaced as soon as possible, however, by a thoracotomy tube for definitive management.

Failure of Lung to Reexpand (Table 5): Patients managed either nonspecifically or by thoracentesis had an average collapse of 34% at the time of hospital discharge. The lungs of only 6% of patients so managed were completely reexpanded.

Those patients, on the other hand, who were treated by thoracotomy tube with water-seal drainage had an average collapse of only 2.5% at the time of hospital discharge. The lungs of 55% had completely reexpanded, and no patient had collapse of more than 10%.

Pleural Effusion: Two cases of pleural effusion were noted, one managed conservatively and the other by thoracotomy tube. Experience with artificial pneumothorax has shown, however, that effusion is not an infrequent complication,

11. Kreutzer, F. L.; Brizzolara, L. G., and Rogers, W. L.: Treatment of Spontaneous Pneumothorax by Means of Continuous Intrapleural Suction, Dis. Chest **21**:663-676 (June) 1952.

with occurrence more likely the longer the pneumothorax is maintained. Similar experiences have been recorded in the case of spontaneous pneumothorax.

Empyema: Except in cases resultant from active tuberculosis, this is an infrequent complication regardless of the primary treatment if adjunctive antibiotic and expectorant therapy are utilized as outlined previously. The longer the fistula remains open the more frequent is such a complication.

Bronchopleural-Cutaneous Fistula: Two cases were recorded in our series, one managed by thoracotomy tube and the other by repeated thoracenteses. It was our impression that in the former instance the tube had either been placed into the ruptured bleb or had engulfed the tube as reexpansion occurred. Such a complication is obviously less likely if no specific treatment is utilized. Pulmonary resection is indicated for this complication.

Hemothorax: Hemorrhage may occur from either the pulmonary parenchyma or the thoracic wall coincidentally with the pneumothorax. The latter source is much more frequent. If bleeding is not controlled by reexpansion of the lung (by means of a thoracotomy tube) open thoracotomy is indicated. The one patient in

TABLE 6.—*Average Hospital Stay in Relation to Treatment*

Treatment	Hospital Stay, Days
No specific treatment	17
Thoracentesis	
Thoracotomy tube with water-seal drainage	10
Thoracotomy	14

our series with such a complication was found to have bleeding from an intercostal artery.

Recurrence: Excision of the pulmonary segment containing blebs appears to be the only certain method of preventing recurrence. Surgery is indicated after multiple recurrences. Recurrence rate is 10 to 30%.[12]

Minimal Hospitalization Time (Table 6): The average hospital stay of patients treated nonspecifically or by thoracentesis was 17 days. Patients managed by thoracotomy tube stayed an average of only 10 days, while those treated by definitive thoracotomy were hospitalized an average of 14 days. The latter two averages include patients originally managed by some other method and eventually treated surgically. For most patients managed initially by surgical intervention, hospitalization averaged only five days.

Early Return to Economic Productivity: Patients treated by thoracotomy tube were allowed to return to work immediately after hospital discharge. We do not have statistics which indicate the period of time before patients treated nonspecifically were allowed to return to work. Discussion with physicians who so treated their patients, however, revealed that bed rest with gradual progressive ambulation was advised for from four to six weeks before the patient returned to work.

12. Palmer, J. P., and Taft, R. B.: Spontaneous Pneumothorax, J. A. M. A. **96**:653-657 (Feb. 28) 1931. Myerson, R. M.: Spontaneous Pneumothorax: A Clinical Study of 100 Consecutive Cases, New England J. Med. **238**:461-463 (April 1) 1948.

SUMMARY

The etiology of spontaneous pneumothorax is obscure in most instances (64%), and the condition must be labeled "idiopathic." In many, if not all, these instances it is due to rupture of subpleural blebs or bullae which may be congenital or the result of local structural changes produced by obstructive emphysema, pneumonitis, cystic bronchiectasis, or tuberculosis. Tuberculosis is an infrequent cause (6%). A history of indirect trauma preceding the collapse is unusual.

Spontaneous pneumothorax with less than 25% collapse should be treated conservatively, the patient being closely observed for progressive collapse. On the other hand, if collapse is greater than 25%, active surgical intervention is the treatment of choice.

Insertion of a Pezzer catheter into the pleural cavity with water-seal drainage can easily be performed with the patient under local anesthesia. The advantages of such treatment are more rapid reexpansion of the lung, early relief of symptoms, prevention of complications, reduction in hospitalization time, and earlier return to economic productivity.

Thoracotomy and definitive surgery, such as resection of blebs, segments, or lobes, are indicated in progressive hemopneumothorax, persistent bronchopleural fistula, and multiple recurrences.

PREVENTION AND MANAGEMENT OF INJURIES TO THE PULMONARY VESSELS DURING PULMONARY RESECTION

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CLEVELAND

INJURY to a pulmonary vessel may be one of the most serious accidents that can occur during the course of a pulmonary resection. If the hemorrhage is uncontrollable or massive, death may occur immediately. If the vascular damage is extensive or if a crushing forceps is applied to control the rapid and severe blood loss, it may be necessary to resect the entire lung when lobectomy or segmental resection was all that was initially planned.

The three current texts on the technique of thoracic surgery [1] all describe a method for careful dissection of the pulmonary vessels. They stress care and state that prevention of injury is very important. Methods of control of hemorrhage are mentioned by Overholt and Langer and by Johnson and Kirby, emphasizing the fact that use of crushing forceps—and consequently further damage—should be avoided. Methods of repair are described. It is under these three headings, prevention, control, and repair, that the problem will be reviewed. While few if any of these principles and methods are original, it is believed that an outline of their systematic application is of value. Accumulated experience will be reviewed with case reports.

PREVENTION

Causes of Injury.—Despite the greatest care in the dissection of the pulmonary vessels, injuries may occur. The basic causes of injuries to the pulmonary vessels during dissection are threefold. The first is the failure to dissect in the proper anatomical plane, which is between the vessel and the perivascular sheath (Fig. 1). The second is the failure to recognize anatomical variations and distortion by inflammatory adhesions and tumor. The third and most treacherous is the change

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1. Overholt, R. H., and Langer, L.: The Technique of Pulmonary Resection, Springfield, Ill., Charles C Thomas, Publisher, 1949, pp. 48, 66, and 67. Sweet, R. H.: Thoracic Surgery, London, W. B. Saunders Company, 1950, pp. 144-145, and 168-170. Johnson, J., and Kirby, C.: Surgery of the Chest, A Handbook of Operative Surgery, Chicago, Year Book Publishers, Inc., 1952, pp. 241-244.

produced around and in the wall of the vessel by pathological processes that make the vessel more friable. These changes include inflammatory reaction, with dense adherence to contiguous lung, pleura, and lymph nodes, and involvement by tumor. The vessels are made "brittle" by these changes as well as by the changes incident to aging.

Technique of Dissection.—After the mediastinal or interlobar pleura has been incised, all small vessels in the areolar tissue should be divided between ligatures. Any oozing should be controlled and cleared away by periodic irrigation with saline. A clean clear field is essential for safe dissection.

When the outlines of the vessel can be seen, the perivascular sheath (Fig. 1 *a*), so well demonstrated by Tocker and Langston,[2] is picked up with a smooth tissue forceps and entered with the tip of a cystic duct forceps, or similar instrument, or incised with a fine dissecting scissors. The sheath is then dissected from the vessel

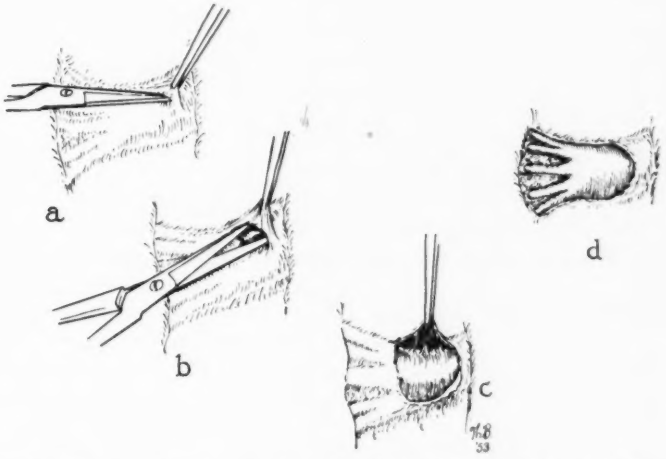

Fig. 1.—Semidiagrammatic representation of method of dissection, showing cleavage plane between the perivascular sheath and the pulmonary vessel.

with the cystic duct forceps or scissors bluntly and divided where necessary longitudinally over the vessel (Fig. 1 *b* and *c*). Only in the severest inflammatory reactions will this be impossible. The dissection in this plane will then invariably proceed quickly and safely and can be carried out onto the vascular branches. A small gauze wad in the tip of a Kelly forceps, a cystic duct forceps, or a blunt-ended dissecting scissors may be used for this purpose, and a clearly delineated vessel is obtained (Fig. 1 *d*).

Vascular surgeons have been aware of the fact that dissection in the adventitial plane is safer and easier. Most thoracic surgeons have discovered this and carry out their dissections this way. We stress this and insist on it when teaching our residents, although at first they feel it is more risky to dissect so close to such large vessels.

2. Tocker, A. M., and Langston, H. T.: The Perivascular Space of the Pulmonary Vessels, J. Thoracic Surg. **23**:539, 1952.

Overholt says that one should always dissect so as to have three sides of any great vessel exposed before completing the dissection. If injury occurs, one can then compress the vessel between thumb and forefinger.

Safe methods of ligation and division of vessels are well illustrated in the above-mentioned textbooks and this aspect of technique will not be described.

Anatomy.—A knowledge of normal pulmonary vascular anatomy as well as the usual variants is essential. An anatomical variation seen occasionally is the small filamentous branch that can arise from either small or large vessels (Fig. 2*a*). These may be mistaken for adhesions and if stripped or pulled away bluntly may cause a serious tear in the parent vessel.

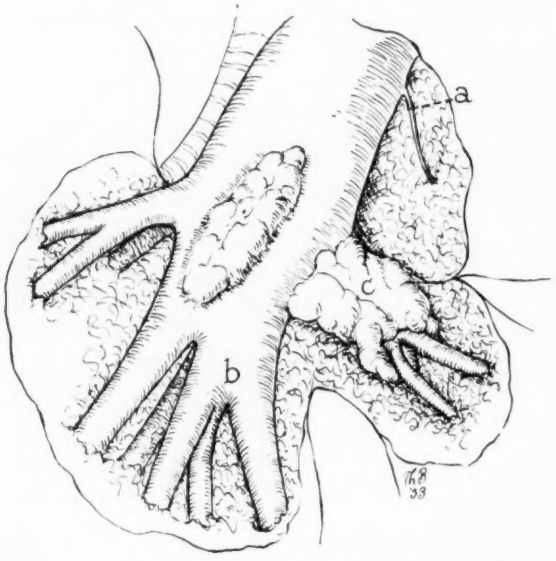

Fig. 2.—Anatomical features that may lead to injuries: (*a*), anomalous filamentous branch from right intermediate pulmonary artery; (*b*), point of division of right inferior pulmonary artery into segmental branches (unseen posterior branch may be perforated); (*c*), branch of artery to middle lobe surrounded by adherent lymph nodes.

Another anatomical point at which injury is prone to occur is the point at which vessels subdivide (Fig. 2*b*). The posterior lying branches may not be seen, and the dissecting instrument may perforate the unseen vessel or the dividing vessel just before it bifurcates or trifurcates. Serious tears may be caused at the point of branching by undue traction during the dissection.

Pathological Changes.—The normal pulmonary vessels are more delicate and more easily injured than corresponding systemic vessels. When pathological changes have occurred adjacent to them or within them, they become even more friable. Once lacerated the tear extends in them with little, if any, additional trauma or manipulation. In the aged; in patients who have had inflammatory reactions in the lung, bronchus, or pleura adjacent to the vessel; in cases in which tumor has

infiltrated into the region, and particularly in cases in which the lymph nodes have become fibrotic and calcified (Fig. 2*c*), dissection must proceed with extreme caution. What seems to be normal and gentle dissection may cause injury.

Technical Preventive Measures.—When difficulty can be anticipated, preliminary control of the artery or artery and veins at the hilum, as suggested by Kergin,[3] may be indicated. We have frequently isolated the main pulmonary artery and placed a heavy ligature around it without tying it down. If injury occurs, the vessel can be quickly controlled by temporary ligation, as described below. In one instance temporary ligatures were applied to the left main pulmonary artery and superior pulmonary vein before removal of a shrapnel fragment from deep in the left upper lobe. The incision through normal lung tissue was bloodless.

CONTROL OF HEMORRHAGE

If one is so unfortunate as to injure a vessel, two things must be kept in mind that require quick and deft action because bleeding is invariably brisk if not massive. First, one must prevent blood loss and possible exsanguination. Second, one must do this in such a way as to make subsequent repair and permanent control of the laceration possible. I still recall the first operative pulmonary hemorrhage I saw in 1936 as an intern. A right pneumonectomy was being attempted for bronchogenic carcinoma. The lesion infiltrated the mediastinum, but an attempt was made to remove the lung. The pulmonary artery was lacerated, and large curved Kelley and Ochsner forceps were applied to control the massive hemorrhage, and the patient was returned to the ward with the clamps protruding through the incision. He died in a few hours of superior vena caval obstruction and shock. Recently, one of our residents had a similar accident and was able to control the bleeding with a piece of oxidized cellulose held down over the hole in the artery by mattress sutures to adjacent mediastinal pleura.

To control most bleeding a finger tip is placed over the laceration, or the laceration is pinched closed between the thumb and finger. After the bleeding has been controlled, the field is cleared of blood and the location and extent of injury determined. If the hemorrhage was originally controlled with the right hand, sometimes it is better to shift hands and use the left for control. This leaves the right hand free for other manipulations, and gives one an unobstructed view and field of action. If control is adequate and working room is sufficient, the laceration can be repaired without further manipulation, as described below. Otherwise, proximal control of the vessels at the hilum by temporary occlusion is necessary. Sometimes the artery and both veins must be controlled. Sometimes the artery proximally and distally can be dissected free and occluded temporarily. Frequently, proximal control of the artery is sufficient. This is determined by the location and extent of the injury.

There are several methods for carrying out temporary occlusion. The simplest is to grasp the vessel between thumb and fingers. The problem of maintaining this with one hand and still getting good vision and sufficient room to work with the other hand makes positive proximal control preferable. The perivascular sheath of the pulmonary artery or vein is entered at the hilus and the vessel quickly dis-

3. Kergin, F. G.: Silicotic and Tuberculosilicotic Lesions Simulating Bronchiogenic Carcinoma, J. Thoracic Surg. **24**:545, 1952.

sected out with the index finger, as described by Rienhoff.[4] A No. 10 or 12F soft rubber catheter can be passed around the vessel and then twisted. A heavy ligature can be tied over a piece of No. 18 or 20F soft rubber catheter (Fig. 3 *a*). If available, a noncrushing clamp, such as the Potts ductus clamp, or a modification, or a Blalock or Crafoord coarctation clamp can be quickly applied (Fig. 3 *b*). If necessary, the portion of the vessel distal to the injury can be occluded with the operator's finger or dissected out and temporarily occluded by threading the encircling ligature through a small piece of rubber and tying over this (Fig. 3 *b*). If this is not possible and back bleeding is severe, one or both pulmonary veins will have to be occluded by one of the aforementioned methods.

Occlusion of the pulmonary artery and/or veins for short periods apparently causes no irreversible change in the lung, as demonstrated experimentally by Davis

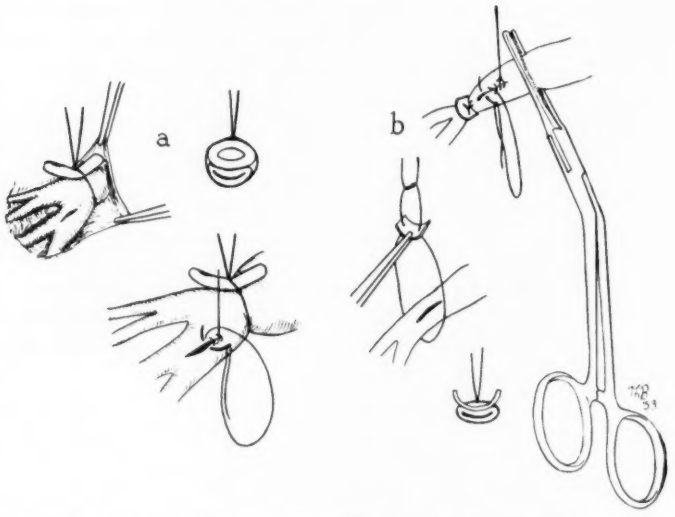

Fig. 3.—Suggested methods for temporary occlusion of the pulmonary vessels (see text).

and his associates [5] and by Hanlon and his associates.[6] So far I have seen no ill effects or evidence of injury to the vessel. The dissection can then be completed if necessary, the injury exposed, and repair carried out.

One means of direct control without proximal occlusion of the vessel has been tried experimentally but never in patients. This was suggested by Dr. Claude Beck. We used a Potts ductus forceps which he had had modified for another purpose. This was curved in a semicircle. It could be applied longitudinally to the artery

4. Rienhoff, W. F., Jr.: A Two-Stage Operation for Total Pneumonectomy in the Treatment of Carcinoma of the Lung, Demonstrating a New Technique for Closure of the Bronchus, J. Thoracic Surg. **8**:254, 1939.

5. Davis, H. A.; Gordon, W. B.; Hayes, E. W. Jr., and Wasley, M. T.: Effect on Lung of Various Periods of Temporary Occlusion of the Pulmonary Artery, A. M. A. Arch. Surg. **64**:464, 1952.

6. Hanlon, C. R.; Sabiston, D. C., Jr., and Burke, D. R.: Experimental Pulmonary Venous Occlusion, J. Thoracic Surg. **24**:190, 1952.

or vein to control a laceration (Fig. 4), but suturing the vessel without causing constriction was difficult. It is suggested that this type of forceps be used to occlude accessible lacerations, and, if suture without constriction is too difficult, the vessel can then be controlled proximally and distally and the forceps removed to allow accurate suture.

Control of hemorrhage from ligatures slipping off short vascular stumps is worthy of mention. The preventive aspects consist of obtaining as long a stump as possible by dissecting out the peripheral branches and placing the distal ligatures here instead of on the main trunk. A transfixion ligature in addition to one or two proximal ligatures should always be used on large vessels. Ligatures should not be placed around the pulmonary veins so close to the pericardium as to include a portion of the pericardium. If this is done the transmitted motion of the peri-

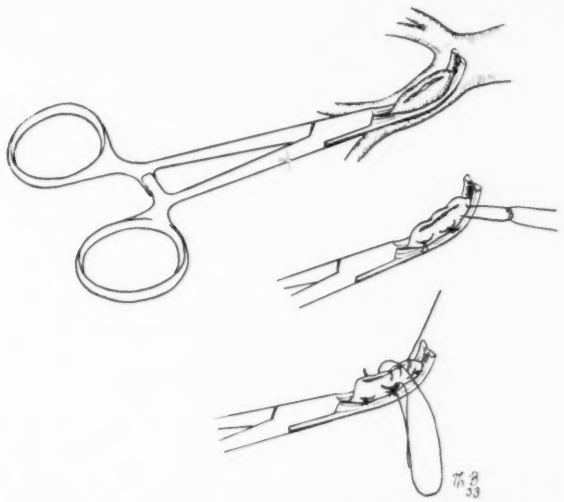

Fig. 4.—Modified Potts ductus clamp used for lateral occlusion of laceration in pulmonary vessel while repair is carried out.

cardium may "shrug" the ligatures off. If the ligatures slip and the stump opens up, the index finger or thumb should be used to plug it if the stump itself cannot be grasped between thumb and finger or occluded by a noncrushing type of forceps, as mentioned previously. The latter is relatively easily done if the stump is long. Again, one must be careful when using crushing hemostatic forceps, as the stump may be lacerated and bleeding may start behind the forceps with disastrous results.

When the extrapericardial portion of the vein is short, intrapericardial ligation may be carried out as described by Allison,[7] or the vein may be tied by a single heavy ligature and the end of the stump closed by continuous over-and-over nonabsorbable surgical (fine silk) sutures in one or two rows. The left pulmonary artery can also be approached within the pericardium for ligation.

7. Allison, P. R.: Intrapericardial Approach to Lung Root in Treatment of Bronchial Carcinoma by Dissection Pneumonectomy, J. Thoracic Surg. **15**:99, 1946.

Finally, if a ligature slips off the vein within the pericardium, the vein can be occluded by placing a Satinsky or Harken auricle clamp across it or across the left atrium itself and closing the stump with the usual double row of continuous 5-0 Deknatel sutures (Fig. 5).

The slipping of ligatures from the distal vascular stumps is common and can cause troublesome back bleeding but is usually not too serious. Overholt recommends use of suture ligatures distally to prevent this. Ligatures will not slip if the distal stump is fairly long. These bleeding vessels may be grasped with the usual hemostatic forceps.

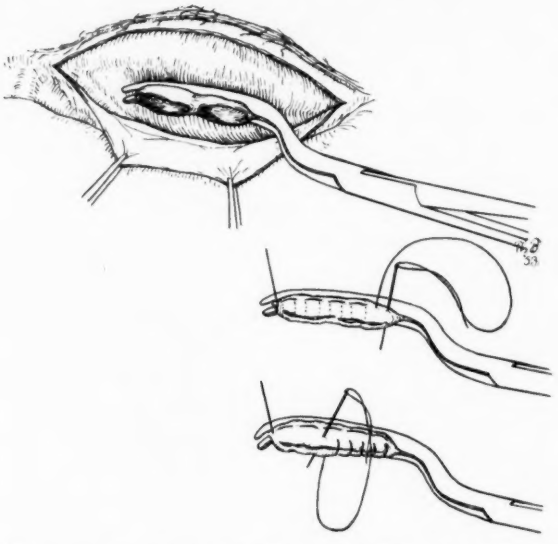

Fig. 5.—Semidiagrammatic representation of intrapericardial control and suture of pulmonary veins with Harken's auricular appendage forceps.

Some mention should be made of the use of the hilum tourniquet to control bleeding. Sweet describes its use in lobectomy in his textbook. I have had little experience with it but am sure that in certain critical instances it may be lifesaving.

REPAIR

Arterial 5-0 Deknatel suture material is used. If the laceration is small, a few interrupted mattress sutures are sufficient. If larger, a single or double row of continuous over-and-over sutures or a bottom row of continuous mattress and second row of continuous over-and-over sutures are satisfactory. Gelfoam may be applied to the suture line, but this is seldom necessary.

If the injury was so severe as to make suture impossible, resection and end-to-end anastomosis of the vessel might be considered. I do not know of this having been done and in such instances it has always been necessary to resect at the next highest level in doing an additional lobectomy or pneumonectomy.

REPORT OF CASES

The following cases represent an experience taken from over 250 lobectomies, pneumonectomies, and segmental resections done for various reasons. With the exception of Case 8, I personally participated in all of these procedures as the surgeon or instructor.

CASE 1.—C. J., a 45-year-old white man, was admitted to Cleveland City Hospital, in 1946, for repeated hemoptysis due to bronchiectasis of the right upper lobe. A right upper lobectomy was carried out on Oct. 23, 1946. The posterior tributaries to the superior pulmonary vein from the upper lobe were being dissected out with a Moynihan gall-bladder forceps when a tear occurred posteriorly. The underlying inferior pulmonary artery was injured when an attempt was made to control the brisk bleeding with a Kelly forceps. The hemorrhage then became massive and the patient exsanguinated even though more clamps were applied at the hilum.

There was undoubtedly a moderately severe fibrosis with some distortion of the normal anatomical relationships at the hilum, but it is felt that both the injury and the fatality could have been averted. The location and presence of the posterior lying branch, as represented in Figure 2 *b*, was not well appreciated. A cleaner dissection within the perivascular sheath would have given better visibility. After the injury occurred, the crushing Kelly forceps should not have been used. Digital pressure at the bleeding point while the superior pulmonary vein and right pulmonary artery were isolated and temporarily occluded at the hilum would have been adequate to control the bleeding. Then the dissection could have been completed safely and leisurely.

CASE 2.—D. C., a 50-year-old white man was admitted to Cleveland City Hospital, in 1948, because of cough and chest pain. Bronchoscopy revealed a bronchogenic carcinoma. A right pneumonectomy was carried out on Aug. 19, 1947. After the pulmonary artery and superior pulmonary vein were divided between ligatures, the bronchus was clamped. The inferior vein was freed but was too short to divide between ligatures. It seemed to be thickened because of involvement by carcinoma. Two proximal ligatures were applied next to each other and the vein divided. Both ligatures slipped off. The pericardium was opened and the pulmonary veins were both isolated. Again, there was very little length. A heavy braided silk ligature was placed around the vein and tied. Again, when the vein was divided within the pericardium, the tie came off. The vein was grasped at its junction with the left atrium with a kidney pedicle clamp, but this injured the vein and bleeding persisted. The patient died of blood loss.

I feel that a noncrushing clamp such as that of Satinsky or Harken would have controlled this bleeding and allowed suture of the short vein stump, as demonstrated in Figure 5.

CASE 3.—F. A., a 51-year-old Negro woman, was admitted to Cleveland City Hospital July 24, 1950, for right middle lobectomy because of persistent cough with occasional hemoptysis. She was known to have bronchiectasis of the middle lobe. At operation the fissure was developed with some difficulty due to the inflammatory reaction and fibrosis from the middle lobe disease and surrounding lymph nodes. The artery was finally well cleaned off. The first artery to the middle lobe was divided between ligatures, and the second artery had one ligature tied around it when it separated from the main artery at its origin. The bleeding was brisk but easily controlled with digital pressure. An attempt was made to close the 2 or 3 mm. opening with a 5-0 Deknatel suture while occluding the artery proximally between the left thumb and forefinger. The exposure was poor, and the suture caused further tearing of the artery, which was quite friable. An Allis forceps was used to try to occlude the tear. This caused further injury, and the tear quickly extended up into the main pulmonary artery. Before adequate

control could be obtained, the blood pressure dropped and the heart stopped. The heart was restarted with massage, and a right tourniquet pneumonectomy was carried out, but the patient died within 24 hours with signs of cerebral damage.

I feel that the injury was due to a pathologically "brittle" artery. If a temporary control ligature had been tied proximally around the main right pulmonary artery, repair of the small opening probably could have been carried out without event because the exposure would have been better and the sutures could have been accurately placed in a collapsed vessel.

CASE 4.—H. L., a 37-year-old white man, was admitted to Brecksville Veterans Administration Hospital on June 21, 1950. His far-advanced bilateral pulmonary tuberculosis was treated with streptomycin, paraaminosalicylic acid, pneumoperitoneum, left pneumothorax, and bed rest. Because of the persistence of bacteria in the sputum and because of evidence of residual cavity in the right upper lobe, a resection was recommended. On June 25, 1951, a right middle and upper lobectomy was carried out through a high posterolateral incision. The lobectomy had been completed and some large fibrocaseous nodes were being removed from the hilum and along the inferior pulmonary artery. The dissection was careful and gentle, but a large rent was made in the artery when a portion of its wall came away along with one of the lymph nodes. The injury was extensive. The main artery was occluded proximally between the left thumb and fingers, while the laceration was closed with a double row of continuous 5-0 Deknatel sutures. The lumen of the vessel was markedly narrowed, but the lower lobe appeared normal by x-ray study, despite a subsequent thoracoplasty.

Studies will be carried out on this man by angiocardiography and bronchospirometry to determine the function of this lobe.

CASE 5.—E. C., a 35-year-old white man, was admitted to Crile Veterans Administration Hospital on May 31, 1951, because of chronic cough productive of 3 oz. (90 cc.) of purulent sputum daily. Bronchograms revealed moderately severe cylindrical bronchiectasis limited to the left lower lobe. On July 3, a left lower lobectomy was carried out through a lateral incision. The dissection of the artery in the interlobar fissure was difficult owing to the marked fibrous adhesions, inflammatory reaction, and adherent lymph nodes. Despite extreme caution the artery was perforated adjacent to the origin of the lingular artery. A ligature was placed around the pulmonary artery at the hilum and tied over a piece of catheter, while the bleeding was controlled by digital compression at the site of injury. The laceration was closed with a continuous 5-0 Deknatel arterial suture. Because the lingular artery was involved by the laceration, this branch was ligated in continuity, but the lingula was not resected. The lobectomy was completed without further event. The patient made a good recovery.

CASE 6.—Mrs. R. B., a 40-year-old white housewife, was admitted to the University Hospitals, on June 10, 1952. She had had cough and sputum for two years and one episode of hemoptysis about one year previously. Bronchograms made elsewhere showed a shrunken middle lobe with bronchiectasis and changes in the basilar segments of the right lower lobe suggestive of early cylindrical bronchiectasis. On June 20, a right middle lobectomy was carried out by the individual ligation technique. The middle lobe was contracted and fibrotic. The fissure between the lower and middle lobes was developed with difficulty because of fibrous adhesions. Fibrocalcific nodes encircled the origin of the middle lobe arteries and bronchus. Therefore the arterial branches and the bronchus to the middle lobes were divided about 1 in. (2.5 cm.) distal to their origin. After the lobe was removed, it was decided to try to shorten this bronchial stump. In trying to free and ligate the middle lobe arteries close to their origin from the inferior pulmonary artery, the latter was lacerated. Bleeding was massive, and it was necessary to clamp the inferior pulmonary artery with crushing hemostatic clamps above and below the tear to prevent exsanguination. The main pulmonary artery was then temporarily ligated at the hilum by tying a ligature over a piece of catheter. The damage to the inferior pulmonary artery was found to be irreparable. The artery was severed and its stump closed with a continuous 5-0 Deknatel suture. A right lower lobectomy was also done, and the patient made an uneventful recovery.

Loss of the right lower lobe could have been prevented if the hilar vessels had been temporarily controlled before the attempt to dissect off the adherent lymph nodes.

CASE 7.—J. S., a 36-year-old white man, had far-advanced bilateral pulmonary tuberculosis which had been treated since 1949 at Brecksville Veterans Administration Hospital. On July 30, 1951, a resection of the left upper lobe and the apical and posterior basilar segments of the left lower lobe was done to remove residual cavities and fibrocaseous disease. An empyema and bronchopleural fistula developed. After one direct attempt at closing the fistula and two thoracoplasties, the fistula and empyema still persisted and the sputum was positive for organisms. The remainder of the left lung was removed on Aug. 8, 1952. The main pulmonary artery had been divided between ligatures, leaving a very short stump. About five minutes later a longitudinal "crack" appeared spontaneously in the stump of the artery proximal to the ties (Fig. 6 *a*). This began to get larger and bleed briskly but was easily controlled with the finger tip while

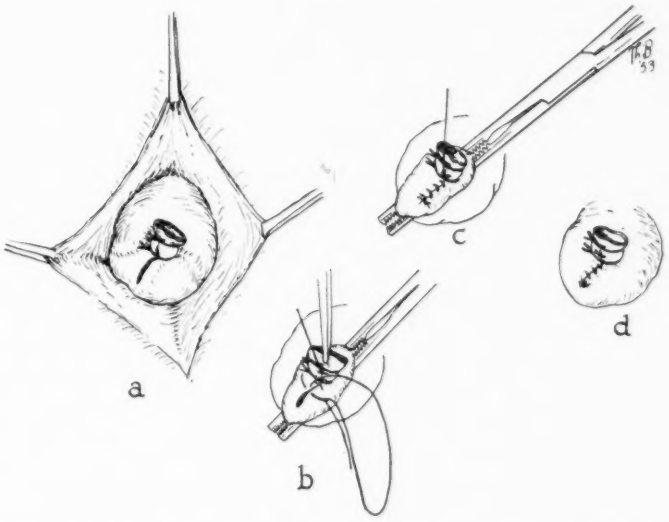

Fig. 6 (Case 7).—Control and repair of spontaneous "crack" in stump of left pulmonary artery.

a Potts ductus clamp was placed obliquely behind it. The 5 mm. "crack" was then easily closed by a double row of 5-0 Deknatel sutures (Fig. 6 *b*, *c*, and *d*). The procedure was completed, and recovery has been good despite the empyema. The sputum is now free from organisms.

CASE 8.—W. S., a 38-year-old Negro man, had been treated for far-advanced bilateral pulmonary tuberculosis at Brecksville Veterans Hospital since September, 1951. In September, 1952, there was still a cavity in the left upper lobe, and the sputum was positive for organisms. Therefore, on Oct. 10, 1952, a left upper lobectomy was carried out in the lateral position. The pulmonary artery was perforated at its junction with the lingular artery. The pulmonary artery was occluded proximally with a No. 12 F soft rubber catheter twisted on itself. The lingular artery was divided between ligatures and the laceration closed with a continuous 5-0 Deknatel suture. The lobectomy was completed without further event.

CASE 9.—W. M., a 52-year-old white man had been treated on and off since 1950 for bilateral pulmonary tuberculosis. He had failed to follow therapy and had relapsed. He was admitted to Sunny Acres Tuberculosis Hospital on April 19, 1952. After six months of intensive therapy, the sputum was still positive for organisms and active disease was limited chiefly to the right

upper lobe. On Oct. 16, a right upper lobectomy was carried out in the face-down position. The dissection of the pulmonary artery in the fissure between the upper and lower lobes was extremely difficult owing to the fibrous reaction produced by the extensive disease. The artery was inadvertantly perforated while dissecting in the fissure. Bleeding was controlled by digital pressure. The main pulmonary artery was temporarily ligated over a catheter at the hilum, and the laceration was closed with a continuous 5-0 Deknatel atraumatic suture. The circulation resumed satisfactorily after removal of the temporary ligature, and the lobectomy was completed without further event. Blood loss was minimal.

CASE 10.—W. R., a 69-year-old white man, was admitted to the University Hospitals on Nov. 25, 1952, because of persistent hemoptysis. No pulmonary lesion was seen by x-ray examination, but on bronchoscopy blood was seen to come from the left upper lobe bronchus. Hemoptysis of fair proportions persisted despite the use of antibiotics and bed rest, and a diagnosis of tumor could not be ruled out. For this reason, a left upper lobectomy was carried out on Dec. 3. No tumor mass was palpable. There was slight thickening around the upper lobe bronchus. There was some difficulty in developing a clean dissection plane between the distal pulmonary artery and the perivascular sheath. Therefore the main pulmonary artery was isolated and a ligature placed loosely about it. While the artery to the apicoposterior segment of the upper lobe was being isolated, a tear was made by the dissecting instrument at the junction of the branch with the main artery. An angulated Potts ductus forceps was used to occlude the previously isolated left pulmonary artery at the hilum, and isolation of the apicoposterior branch was completed with very little bleeding. After this vessel was divided between the ligatures, the small rent was easily closed with two 5-0 Deknatel mattress sutures. The remainder of the procedure was uneventful, and blood flow resumed when the ductus forceps was removed. The postoperative course was satisfactory.

CASE 11.—A. C., a 48-year-old Filipino man, had been treated since 1949 for far-advanced bilateral pulmonary tuberculosis. The right upper lobe was almost completely cavitated. Despite extremely poor pulmonary function, it was decided to do a right upper lobectomy. This was done on Jan. 29, 1953, at Sunny Acres Tuberculosis Hospital. The face-down position was used. The lobe had to be freed from the chest wall by extrapleural dissection. The hilum was difficult to expose owing to the dense adhesions from the lung to the mediastinal pleura, but the upper lobe bronchus and right main pulmonary artery were finally identified and isolated. The bronchus to the upper lobe was divided and its proximal stump closed with sutures. Fairly large arteries to the apical, anterior, and posterior segments of the upper lobe were isolated and divided between ligatures. As the dissection was continued down the artery into the fissure between the upper and lower lobes, adherent lymph nodes were encountered. A small additional anomalous artery was seen coursing to the upper lobe through these matted nodes. Moderate traction was being maintained on the severed distal upper lobe bronchus, but this was sufficient to tear this small branch away from the main artery. Bleeding was immediately controlled by digital compression, while the artery was controlled proximally at the hilum with a heavy silk ligature tied over a piece of catheter. Repair of the laceration was then easily accomplished with two rows of continuous over-and-over 5-0 Deknatel sutures. The ligature was removed from the artery at the hilum, and blood flow resumed. The lobectomy was completed without event. The patient's immediate postoperative course was satisfactory. He subsequently died of an empyema and bronchopleural fistula.

COMMENT

Injury to pulmonary vessels during resection can be prevented by careful dissection in the proper anatomical plane. When difficulty can be anticipated because of pathological change, preliminary control of the main vessels at the hilum should be carried out.

When injury occurs, vessels should not be clamped with crushing clamps unless absolutely necessary to prevent exsanguination. Digital control of the bleeding point followed by temporary proximal control of the main vessels at the hilum can be carried out to allow accurate repair of the injury by vascular suture.

In certain instances noncrushing types of forceps, such as the Potts ductus forceps or Crafoord aortic occlusion forceps, will be of inestimable value in managing these injuries. A modification of the Potts ductus forceps devised by Beck is suggested for control of lacerations in vessels.

Our experience with 11 patients includes 3 who died and 8 in whom satisfactory control and repair were obtained. In only one of these eight was it necessary to resect additional pulmonary tissue. In 2 of the 11 patients the causative factor was involvement with carcinoma. In the remainder the primary factor was involvement by inflammatory changes. Two patients had bronchiectasis of the middle lobe; one had bronchiectasis of the lower left lobe. Five had pulmonary tuberculosis. Two of the injuries involved a pulmonary vein and were fatal. The remainder involved the pulmonary artery. It is felt that all of the deaths could have been prevented and that the single case in which a lower lobe was sacrificed could have been handled so as to avert this.

SUMMARY

The cause of injury to the pulmonary vessels during pulmonary resection are listed.

Methods of prevention of injury, control of hemorrhage, and repair of the injured vessels are outlined.

Experiences with three fatal and eight successfully repaired pulmonary vascular injuries are reported.

DISCUSSION

On Papers of Dr. Rapport and Dr. Mendelsohn

Dr. John S. Harter, Louisville: I should like to discuss the paper by Rapport on "Spontaneous Pneumothorax."

I do not believe he goes quite far enough to solve the problem of the patient who is having repeated spontaneous pneumothorax.

To illustrate, we had a patient recently who had lived in Chicago all of his life and who came to Louisville. He had had one or two spontaneous pneumothoraces at a time, over a period of some years. He had been treated at the Veterans Administration Hospital, Hines, Ill., by the technique outlined by Rapport, of inserting catheters. He immediately had a pneumothorax on arriving in Louisville. Because of his history, the thorax was opened for the procedure of obliterating the pleura, which I will go into in just a minute.

When the thorax was opened, there were practically no adhesions. He was out of the hospital only a few days when a spontaneous pneumothorax occurred on the contralateral side, which was also opened and there were practically no adhesions on that side.

What we have been doing over the past number of years was going back to the technique used originally in lobectomies in the early 1930's (when we had no antibiotics), of attempting obliteration of the pleural cavity. As you remember, it was felt necessary to obliterate the pleural cavity in the early days of lobectomy because of the fear of contamination of the pleura. The method was to wipe both the visceral and the parietal pleurae with dry gauze and to reexpand the lung to produce adhesions.

The adhesions produced by this method do not restrict the lung in motion. They are mostly avascular, but they do produce a very good obliteration of the pleural cavity.

I suppose we have done this on about 35 patients; I do not have the exact figures. In none of them has there ever been any recurrence.

Dr. Richard H. Meade, Grand Rapids, Mich.: Dr. Rapport has presented the subject of spontaneous pneumothorax very well, as far as he went, as Dr. Harter said.

I think most of us feel that in the majority of cases of spontaneous pneumothorax which do not immediately clear up with medical treatment, the best treatment is by catheter drainage.

An important point has been stressed before, and it should be stressed again, and that is that some persons have a recurrence of their pneumothorax. I do not think they have a recurrence after a catheter has been placed in the pleural cavity. I think if treatment is by decompression, by needle, these persons can have recurrence.

In my experience, I have very seldom had the chance to treat patients with uncomplicated cases of pneumothorax. I have had the opportunity to operate on 12 patients with chronic spontaneous pneumothorax. Dr. Rapport did not mention such cases in his group, but they do occur. I have encountered only 12 cases of spontaneous pneumothorax in 10 years, but they are frequent enough in occurrence to be of importance.

In a series which I followed, the longest duration of the pneumothorax was 18 months, and in most cases the pneumothorax lasts between four and six months. All except two patients with this condition were seen during the war in the Army. Six of those patients were found at operation to have lungs which could not reexpand unless decortication were done. That was done in each instance. All those patients recovered and have gotten on well since then.

Brock, in 1946, reported on 46 patients with chronic recurrent pneumothorax. He treated them simply by injection (most of them, not all of them) of silver nitrate into the pleural cavity, producing a pleuritis. In none of his patients was the lung encased in an inelastic membrane. I do not know why I should have had 50% of my patients needing decortication, while he, in his larger experience, had none.

In certain other patients, of course, simple drainage does not suffice and thoracotomy will be necessary.

[Slide] This is a picture taken at operation, showing the upper part of the area from which the air was escaping. The lower part shows the lung encased in the inelastic membrane.

[Slide] This next slide shows the membrane lifted up during the process of decortication.

[Slide] The last slide shows the lung fully expanded.

DR. AUGUST F. JONAS, Erie, Pa.: My colleagues and I have been interested in the subject of spontaneous nontuberculous pneumothorax for several years and agree with Dr. Rapport and his co-workers that surgical intervention is the most effective and the most conservative method of management. In order to appraise the situation from the economic viewpoint, we asked our social service department to go over the records of all patients admitted to the hospital with this condition, whether treated medically or surgically, in order to estimate the costs involved. For fairness in comparison—since it was a relatively small group and since their economic and occupational situations varied considerably—we calculated the total cost of hospitalization at Blue Cross and Blue Shield rates and the time lost from work at the prevailing average industrial rates. Our findings show that, economically, it is appreciably cheaper to employ surgical rather than medical therapy for this condition.

TECHNIQUE FOR EXTERNAL DRAINAGE OF THE BILIARY TRACT WHICH LEAVES DUCTS INTACT

An Experimental Study

JOHN H. GRINDLAY, M.D.
JOHANNES EBERLE, M.D.
AND
WALTMAN WALTERS, M.D.
ROCHESTER, MINN.

TECHNIQUES developed for certain purposes are sometimes found to have other applications. The purpose of this study was to determine whether an instrument and technique, developed by one of us (J. H. G.) for the placement of plastic catheters in veins of internal organs of dogs,[1] had promise as a clinical surgical technique for placement of a tube in the extrahepatic bile ducts as a prosthetic device to prevent contraction at the site of a biliary intestinal anastomosis. In the technique we planned to test in dogs, a tube would lead from the external surface of the body through the abdominal wall and surface of the liver, and thence by way of hepatic ducts of increasing size to the common duct, to terminate either there or in the duodenum beyond. It was expected that such a tube could be kept in place for as long as one wished and could be removed without great difficulty and without another operation. The possible disadvantages of the technique appeared to be that the tube might obstruct the peripheral hepatic ducts, causing more or less hepatic damage, and that the opening left in the surface of the liver when the tube was removed might prove undesirable. On the other hand, the fact that no opening would be left at the site of the biliary intestinal anastomosis when a tube was removed seemed to be an advantage which the technique would have over the T-tube technique, the most widely used technique which provides for external biliary drainage.

TECHNIQUE

Polyvinyl copolymer (Transflex) tubes [2] were placed in the biliary tract of dogs by means of metallic introducers, made of rods of polished brass or bronze, 9 in. (22.9 cm.) long, which could be attached to one end of the tubes. The introducer for each particular size of tube was

Read at the Tenth Annual Meeting of the Central Surgical Association, Chicago, March 6, 1953.

From the Section of Surgical Research (Dr. Grindlay) and the Division of Surgery (Dr. Walters), Mayo Clinic, and Fellow in Surgery, Mayo Foundation (Dr. Eberle).

1. Bollman, J. L., and Grindlay, J. H.: Measurement of Renal Gluconeogenesis, Am. J. Physiol. **170**:38-44 (July) 1952. Grindlay, J. H.; Thors, R., and Bollman, J. L.: Effect of Occlusion of Vessels Entering the Liver on Hepatic Venous Pressure in Normal and Cirrhotic Dogs, in Surgical Forum: Proceedings of the Forum Sessions Thirty-Eighth Clinical Congress of the American College of Surgeons, New York, Sept. 12, 1952, Philadelphia, W. B. Saunders Company, 1953.

2. Transflex tubing was furnished by the Irvington Varnish and Insulation Company, N. J.

designed so that a tube could be attached to one end without difficulty but could be detached only by use of considerable force. In addition, the introducers were designed so that when they were attached to tubes the line of junction between catheter and introducer could not be felt with the fingers. For smaller sizes of tubes, stock brass rods, 9 in. long with a diameter slightly greater than the outside diameter of the tubes were used. The introducers for large tubes were made of bronze and were 9 in. long. For a distance of 8 in. (20.3 cm.) from the tip the diameter was ⅛ in. (0.3 cm.) The diameter of the remaining length of the introducer (1 in. [2.5 cm.]) increased gradually to a diameter slightly greater than that of the tube to which it was to be attached. The tips of all sizes of introducers were ground to smooth rounded points. Fittings for tubes were made by machining the other ends of the introducers for a short distance (from ¼ to ⅜ in. [0.64 to 0.96 cm.]) so that this end was transformed into a hose type of fitting. When an introducer was used, it was bent into a curve which approximated that of the direction it would take through the liver.

Introducers which were only 4 in. (10.2 cm.) long and had sharper points were made for each size of tube. These were used in place of the long introducers to pierce the abdominal wall and to pull the free end of the tube to the outside.

All operations were performed with aseptic surgical technique. Ether was used as the anesthetic agent. Exposure of the extrahepatic biliary tract for the placement of tubes was accomplished by opening the right pleural cavity through the 10th interspace and by an L-shaped incision in the right side of the diaphragm.

When tubes were placed in normal dogs, cholecystectomy was performed first. The tip of the introducer with the tube attached was then inserted through the open end of the cystic duct into the common duct. It was guided down the duct and into the duodenum. With slight force the tip was pushed through the duodenal wall. The rest of the introducer and a short length of tubing were pulled out of the duodenum through the small puncture hole. Next, the introducer was detached and placed on the other end of the tube. To do this, the duodenum was incised. Then the portion of tube projecting from the duodenum was grasped and a greater length of tube was pulled out of the duodenum. This caused the tube and introducer to be pulled backward through the cystic duct. They were pulled farther backward until the tip of the introducer could be palpated in the common duct and no farther. By this time most of the introducer had been drawn through the opening in the duodenum. After the cystic duct was ligated, the tip of the introducer was pushed gently into the largest hepatic duct and as far into the liver as possible, a distance which was never more than 2 cm. The tip was then forced through liver substance to the surface of the lobe. It was grasped when it projected from the liver and was withdrawn until the distal end of the tube was at the desired level. In some dogs this level was in the lower end of the common duct; in others, within the duodenum. The tubing was fixed in position by a suture placed in the liver surrounding the tube at its point of emergence and by wrapping and tying the long ends of the suture several times around the tube. A piece of moist polyvinyl sponge (Ivalon surgical sponge [3]) was included in the suture placed in the liver. The small opening in the duodenum was closed, and the free end of the tube was led through the anterior portion of the abdominal wall by the introducer designed for this purpose.

The technique used for obstruction of the common duct has long been used in our laboratory and produces gradual and nearly complete obstruction within one to three months. After an abdominal incision cholecystectomy is performed, the common duct is crushed near its lower end, and a heavy cotton ligature is placed around the duct at this point. The ligature is tied over the tip of a mosquito clamp. The combination of injury to the duct and the irritation produced by the loose ligature appears to cause gradual constriction by a dense band of fibrous tissue.

The same transdiaphragmatic exposure was used for repair of strictures and placement of tubes as was used for introduction of tubes in the biliary tract of normal dogs. The common duct above the stricture and the hepatic ducts were greatly dilated. In one dog the duct was divided above the stricture, and an end-to-side choledochoduodenostomy was performed; in the other dogs a side-to-side anastomosis was made. Two of the latter type of anastomosis were made with a single row of interrupted serosal sutures; in all other dogs the anastomosis was made with an additional row of mucosa-to-mucosa sutures.

3. Ivalon surgical sponge was furnished by the manufacturer, Ivano Inc., Chicago.

After an opening had been made in the duodenum and the posterior row of sutures of the choledochoduodenostomy had been placed (Fig. 1), the point of an introducer was inserted into the common duct and directed through the common and hepatic ducts and for some distance into a lobe of the liver. When resistance was encountered, which was close to the surface of the liver in this group of dogs, the tip was forced through the remaining tissue and the introducer extracted. The other end of the tube was then inserted into the duodenal stoma and directed downward until the tip was in the third portion of the duodenum. After the anterior sutures of the anastomosis of the duct to the duodenum had been placed and tide, the tube was anchored to the surface of the liver and the free end was brought to the surface of the abdomen. A second transflex tube of smaller diameter (No. 20) was placed in the biliary tract in some dogs; in these, the distal end of the smaller tube was in the common bile duct above the anastomosis and the tube emerged from the liver through the hepatic duct of a lobe other than the one from which the larger tube emerged.

All dogs were offered the regular kennel diet. None received special diets or care. The weight and the concentration of serum bilirubin [4] were determined at weekly intervals for four

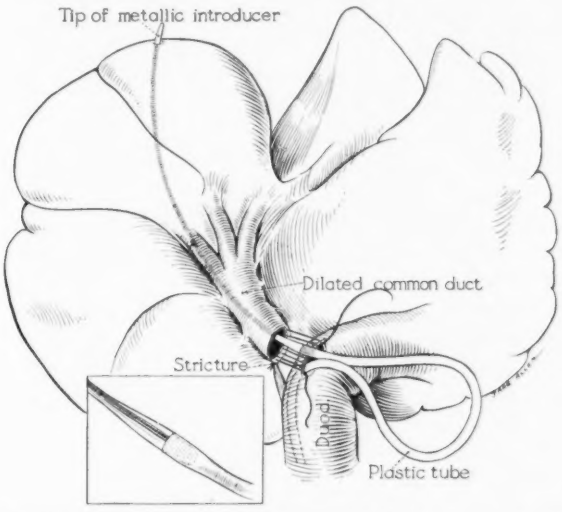

Fig. 1.—Technique for placing a tube in biliary tract of dogs by means of metallic introducer (inset) and manner in which tube is firmly attached to introducer. Larger drawing shows posterior row of sutures of choledochoduodenostomy in place. Introducer has been guided up through dilated common duct and hepatic duct and then pushed through remaining short distance to surface of liver. Tip of introducer will be grasped and pulled out and tube will follow. Distal end of tube has been inserted through duodenal stoma. When anastomosis is completed, a short length of tube will be left in duodenum, while remainder will lie in biliary tract and liver and will lead through abdominal wall to surface.

weeks after operation and thereafter at intervals of a month. Necropsy was performed on all dogs which died or were killed. Histologic examination was made of tissue taken from the liver in several regions, including the region of the tube, as well as from the common duct and from the site of choledochoduodenal stoma.

RESULTS

Normal Dogs.—A single small-diameter polyvinyl copolymer (No. 20 Transfer) tube was placed in each of four normal dogs. A week after operation all had

4. Giordano, A. S., and Prestrud, M.: An Improved Method for the Photelometric Determination of Serum Bilirubin, Am. J. Clin. Path., Tech. Supp. **2**:100-103 (May) 1938.

begun to gain weight, and all weighed as much four weeks after operation as they had before operation. The concentration of serum bilirubin was normal for each dog, never more than 0.5 mg. per 100 cc. One dog was anesthetized and killed at one month; another, at four and a half months, and the remaining two, at six months after operation. All tubes were *in situ*, although the tubes of the two dogs killed after six months had been severed at the skin surface and the ends had retracted through the abdominal wall; one of these dogs had pulled and bitten off the tube four days after operation; the tube of the other had been cut off and allowed to retract one month after operation.

There were no signs of infection about tubes in the dogs in which the tubes had been retained. The tubes were firmly anchored where they emerged from the liver by the fibrous tissue which had grown into the polyvinyl sponge from the liver and encased the ligature which had been tied several times around the tube. A thin layer of fibrous tissue surrounded the tubes in their course through the liver until they entered the hepatic ducts. The hepatic and common ducts were dilated to a diameter approximately three times normal. The walls of the ducts, including those traversed by tubes, appeared grossly to be of normal thickness, and their mucosal linings appeared normal.

Histologic study revealed normal liver in all regions examined except for a zone a few millimeters thick surrounding the thin fibrous tissue sheath which had formed about the tube. In this thin zone there was marked fibrosis. The mucosa of all the ducts, including the common duct, which were examined, was intact and contained occasional clusters of lymphocytes in the submucosa. The fibrous tissue in the walls of the larger ducts had increased slightly from normal.

Dogs with Strictures.—Strictures of 12 dogs were repaired; this usually was done five weeks after the preliminary operation in which the gall bladder was removed and the common duct injured. At the time of the second operation all of the dogs showed signs of obstruction of the lower part of the biliary tract, namely, anorexia, jaundice, and light-colored stools. Values for serum bilirubin were increased to between 2.0 and 26.0 mg. per 100 cc. Most dogs had lost approximately 10% of their body weight.

One aged dog recovered and was well for two months, then became ill and died a week later. In this dog a large (No. 12) tube which extended into the duodenum and a small (No. 20) tube which ended in the common duct had been placed. A small abscess (3 cm. in diameter) which had ruptured and produced peritonitis surrounded the tract of the latter tube where it had emerged from the liver; remnants of roundworms and a short coiled length of tube were found in the abscess, and many roundworms were found in the biliary and upper part of the enteric tracts. Except for these lesions the liver was not abnormal; the stoma was widely patent, and the bile ducts were thin-walled and greatly dilated.

The other 11 dogs recovered after the operation for stricture and remained well. Jaundice disappeared rapidly, and values for serum bilirubin returned to normal within two weeks and remained normal. All the dogs gained weight. Five dogs were anesthetized and killed after three to five months of observation, and six dogs are living and in good health four to six months after operation.

Four of the five dogs which were killed and were examined at necropsy had severed or pulled their tubes out between three and five weeks after operation. Two

tubes, a small one which terminated above the anastomosis and a large one which terminated in the duodenum, were placed in two dogs. In one of these two dogs the tubes had been severed at the skin but internally were still *in situ* at the time of necropsy, four months later. The appearance of the liver and ducts was the same in this dog as in the dogs which had pulled out their tubes, and the tubes fitted loosely in the ducts. The diameter of the ducts was approximately the same in all dogs, a diameter of about 1 cm. for both the common duct and the stoma. In four of the five dogs a side-to-side anastomosis between the duct and duodenum had been made; in one, the anastomosis was end-to-side. Walls of the ducts were thickened but were flexible and not indurated or edematous (Fig. 2). The mucosa at the

Fig. 2.—Opened duodenum and common duct and hepatic duct four months after operation. In this dog, tube was pulled out after it had been in place five weeks. Wide opening between duodenum and dilated common duct is shown, as is opened hepatic duct which tube followed into liver.

anastomosis and in the ducts was intact and appeared normal. Histologic study showed normal mucosa and scattered lymphocytes, occasionally in clusters, in the submucosa. A few scattered lymphocytes were present in the thickened layer of mature-appearing fibrous tissue of the wall. There was no break in continuity of the mucosa of the common duct and duodenum at the choledochoduodenal stoma in any of the dogs, including the dog with the tubes still present.

The surface and cut surface of the liver of the five dogs appeared normal, whereas at the time of anastomosis the capsular surface appeared granular. The fibrous tissue scar which extended from the surface toward the hilus was only 1 mm.

thick in the region through which small tubes had been placed but had been pulled out three to four months before necropsy. The scar representing the path of the large tubes which had been pulled out was 1 to 2 mm. in diameter. Sections of liver revealed a great increase in fibrous tissue in a zone 2 to 3 mm. wide about these scars; dilated ducts, containing inspissated bile, and small areas of healed biliary cirrhosis were seen in a few sections from this zone. Except for these areas the remainder of the liver appeared normal in two dogs; in the other three, there was slight increase in fibrous tissue in the periportal spaces.

The tubes were removed from two of the six living dogs, through small surgical incisions, by cutting them free from the fibrous tissue which united tube, ligature, plastic sponge, and liver capsule; one dog had two tubes which were removed after 11 weeks; the other dog had a single tube which was removed after 14 weeks. The dogs have remained free from signs of biliary obstruction. In each of the other four living dogs a single large tube is still in place, between four and five months after the operation. The ends of these tubes were placed subcutaneously so that they would not be pulled out accidentally and could be kept in place six months or longer.

A mucosa-to-mucosa anastomosis was not made in two dogs in which tubes are still present. Instead, only a few interrupted serosal sutures were used for the anastomosis. These dogs recovered and are as well as those in which the more exact anastomosis was made.

Tubes.—The tubes which were placed in the biliary tract were not used for purposes of drainage of bile, for irrigation, or for instilling solutions or suspensions. A plug was placed in the external end of each tube at the time of operation in all the normal dogs and in the dead or killed dogs which had strictures of the common duct. Once a week, when the dogs were weighed and blood was taken for determination of serum bilirubin, these tubes were flushed with water. However, two of the four normal dogs and four of the five dogs which had had strictures severed their tubes or pulled them out. Tubes of these dogs remained patent as long as the tubes were available for flushing. The outer ends of tubes of the six living dogs were occluded and buried under the skin at the time of operation. In two of these six dogs the tubes were removed later surgically. Leakage of bile from or about tubes did not occur before or after the tubes were removed. Drainage of puriform material about tubes was so slight as not to be noticeable.

Tubes which had been *in situ* for a time and then were removed were no longer transparent but were opaque. They were hard and much stiffer than when they had been implanted, but they were not weak or brittle. At necropsy it was noted that the tubes retained the configuration of their course from the body surface through the biliary tract even after they had been removed; when the tubes had been removed and were bent, they returned quickly to this configuration once the bending pressure was released.

COMMENT

Early in this investigation it was decided that it was impracticable to make use of the tubes for studies on bile, which might be collected from the tubes, or for infusions into the tubes. It seems expedient first to study what effects the presence of a tube which coursed from the duodenum through the extrahepatic and intrahepatic biliary tracts, through liver tissue, and finally to the external surface of the body might have on adjacent tissues, and what interference a tube in this

anatomic position might have with the internal flow of bile when it was present for weeks or months. For these reasons also, the effect of tubes on prevention of recurrence of a stricture at the site of anastomosis was not a primary objective. Nor was it within the scope of the study to test the tube in various types of biliary-intestinal anastomoses or end-to-end anastomosis of bile ducts.

The cutting of holes in the sides of tubes so that the portion of tube distal to the hole might serve as a conduit for bile was considered but rejected for two reasons: 1. Since both sizes of tubing used in the study were much smaller and thinner-walled than any used in clinical surgery, the cutting of a hole might weaken the tube or cause it to kink. 2. In a similar study on dogs,[5] one of us (J. H. G.) had found that plastic tubes implanted in an anastomosis between the common duct and the duodenum become loosely plugged with solid material in time, and yet "liming" did not occur on the outer wall of these plastic tubes and bile seemed to flow without impedence between the walls of the tube and duct. In the present study it is clear that although no bile could flow through the lumen of tubes there was an adequate flow around the tubes.

In addition to the larger tube which ended in the duodenum, a second, smaller, tube which ended in the common duct above the anastomosis was placed in a few dogs. The second tube appeared to be well tolerated, and it would seem from these experiments that a second tube so placed could be implanted if one wished to inject antibiotics, bile, or other liquids into the biliary tract above the level of an anastomosis.

The degree of dilatation of bile ducts in the normal dogs, dogs in which small tubes were implanted and cholecystectomy performed, was not much greater than that usually seen in dogs several months after the gall bladder has been removed. Likewise, the degree of dilatation of ducts seen in dogs which had strictures at the times when the tubes were implanted was not greater than when good drainage of the biliary tract is established by anastomosis alone. The results of the present study appeared to be superior to the results of our earlier studies[6] on anastomosis of the common duct in dogs by other techniques in respect to prevention of recurrence of stricture at the site of the anastomosis, in respect to histologically demonstrable continuity of the mucous membranes of duct and duodenum, and in respect to mortality and morbidity.

Leakage of bile from the liver did not occur when the tubes were severed at the surface of the skin by the dogs, were pulled out, or were removed surgically, nor were there abscesses or adhesions found at necropsy on the surface of the liver indicating that leakage of bile had occurred. In the aged dog which was well for a time and then became ill and died of a hepatic abscess and peritonitis, the abscess on the surface of the liver appeared to be caused by roundworms. At necropsy worms filled the upper part of the enteric tract and fragments were seen in the abscess of the liver. In our experience, roundworms, if they are present in the stomach of dogs, are always found in the bile ducts above an anastomosis between the common duct and duodenum. It is possible that the dog in the present study

5. Grindlay, J. H.: Unpublished data.

6. Musgrove, J. E.; Grindlay, J. H., and Karlson, A. G.: Intestinal-Biliary Reflux After Anastomosis of Common Duct to Duodenum or Jejunum: An Experimental Study, A. M. A. Arch. Surg. **64**:579-587 (May) 1952. Grindlay.[5]

pulled a tube out of its tract through the liver and severed it, that a portion of the tube was left on the surface of the liver, and that roundworms emerged from the biliary tract along the tract left by the tube.

The minimal degree of acute or chronic inflammatory reaction which was found along the course of tubes through the biliary tract may be attributed partly to the fact that the tubes were of plastic and not of rubber. It has been reported [7] that rubber tubes in the biliary tract incite a chronic inflammatory reaction in the walls of ducts.

The passage of the metallic introducers through ducts and parenchymal tissue of the liver was always a simple maneuver and never caused hemorrhage from the wound on the surface of the liver. Likewise, there was no evidence that hemorrhage occurred when tubes were removed. Occlusion of the tract through the liver was apparently rapid.

SUMMARY

A flexible plastic tube was placed surgically in the biliary tract of each of a series of dogs by attaching it to a special metallic introducer having about the same diameter as the tube. The introducer was guided from the duodenum through the biliary tract into the liver, then forced through the liver to its surface, and finally through the abdominal wall. The tube was drawn behind the introducer and left in position within the pathway followed by the introducer from duodenum to surface of the skin.

Tubes of small diameter were placed in the biliary tract of four normal dogs at the time of cholecystectomy. After these dogs were observed for one to six months, they were anesthetized and killed. Examination showed minimal reaction along the tract of the tube.

Larger tubes were placed in the biliary tract of 12 dogs, in each of which a stricture of the common duct had been produced by a previous operation, at the time of choledochoduodenostomy. Six of these dogs are alive and well four to six months after operation; four of these dogs still have the tubes in place; two of the dogs underwent surgical removal of the tubes about three months after placement. One dog died of an abscess produced by roundworms. The remaining dogs were killed in three to five months after operation. The anastomosis in each dog was healed and the stoma was widely open and was lined by an intact layer of normal mucosa. Acute lesions in the ducts and livers produced by the previous strictures had healed.

7. Lary, B. G., and Scheibe, J. R.: The Effect of Rubber Tubing on the Healing of Common Duct Anastomoses, Surgery **32**:789-795 (Nov.) 1952.

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references:

1. A. W. Spittler, Col., (M.C.), U.S.A., J. J. Brennan, Lt. Col., (M.C.), U.S.A., J. W. Payne, Capt., U.S.A.F. (M.C.), American Academy of Orthopedic Surgeons, Jan. 26-31, 1952, Chicago, Illinois.
2. M. C. Cobey, M.D., F.A.C.S., Professor of Orthopedic Surgery, Georgetown University and Senior Attending Orthopedic Surgeon, Children's Hospital, Washington, D.C., The American Surgeon, Vol. XVIII, No. 4, April, 1952, pp. 413, 415.
3. M. C. Cobey, M.D., F.A.C.S., Washington, D.C., private communication.

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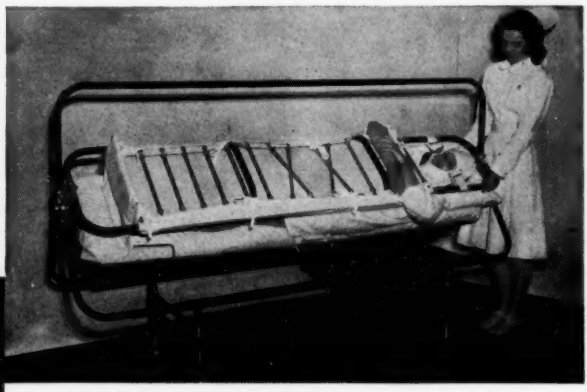

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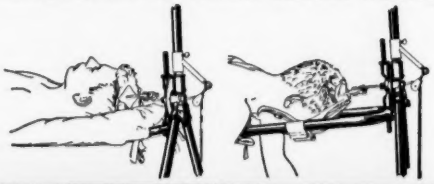

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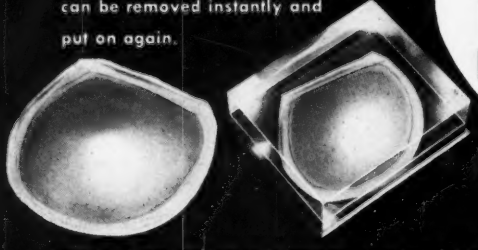

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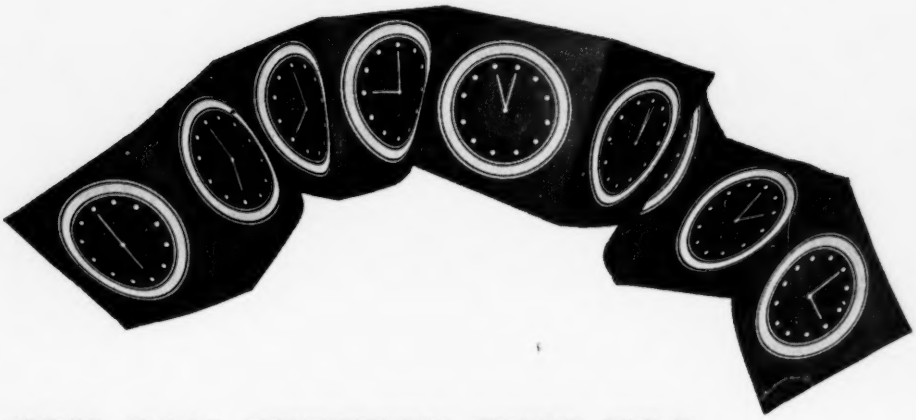

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*Bonica, J. J.: J.A.M.A., 150:1581, Dec. 20, 1952.